

THERAPEUTIC AGENTS USEFUL FOR TREATING PAIN

This application claims the benefit of U.S. Provisional Application No.

5 60/391,962, filed June 28, 2002; U.S. Provisional Application No. 60/411,030, filed
September 17, 2002; U.S. Provisional Application No. 60/413,148, filed September 25, 2002;
and U.S. Provisional Application No. 60/416,582, filed October 8, 2002, each of which is
incorporated herein by reference in its entirety.

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1. FIELD OF THE INVENTION

The present invention relates to Cyanoiminopiperazine Compounds,
compositions comprising an effective amount of a Cyanoiminopiperazine Compound and
methods for treating or preventing pain, urinary incontinence (UI), an ulcer, inflammatory-
bowel disease (IBD), irritable-bowel syndrome (IBS), an addictive disorder, Parkinson's
15 disease, parkinsonism, anxiety, epilepsy, stroke, a seizure, a pruritic condition, psychosis, a
cognitive disorder, a memory deficit, restricted brain function, Huntington's chorea,
amyotrophic lateral sclerosis (ALS), dementia, retinopathy, a muscle spasm, a migraine,
vomiting, dyskinesia or depression, comprising administering to an animal in need thereof an
effective amount of a Cyanoiminopiperazine Compound.

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2. BACKGROUND OF THE INVENTION

Pain is the most common symptom for which patients seek medical advice and
treatment. Pain can be acute or chronic. While acute pain is usually self-limited, chronic
pain persists for 3 months or longer and can lead to significant changes in a patient's
25 personality, lifestyle, functional ability and overall quality of life (K.M. Foley, *Pain, in Cecil
Textbook of Medicine* 100-107 (J.C. Bennett and F. Plum eds., 20th ed. 1996)).

Moreover, chronic pain can be classified as either nociceptive or neuropathic.
Nociceptive pain includes tissue injury-induced pain and inflammatory pain such as that
associated with arthritis. Neuropathic pain is caused by damage to the peripheral or central
30 nervous system and is maintained by aberrant somatosensory processing. There is a large
body of evidence relating activity at both Group I metabotropic glutamate receptors, i.e.,
metabotropic glutamate receptor 1 ("mGluR1") and metabotropic glutamate receptor 5
("mGluR5") (M.E. Fundytus, *CNS Drugs* 15:29-58 (2001)), and vanilloid receptors ("VR1")

(V. Di Marzo *et al.*, *Current Opinion in Neurobiology* 12:372-379 (2002)) to pain processing. Inhibiting mGluR1 or mGluR5 reduces pain, as shown by *in vivo* treatment with antibodies selective for either mGluR1 or mGluR5, where neuropathic pain in rats was attenuated (M.E. Fundytus *et al.*, *NeuroReport* 9:731-735 (1998)). It has also been shown that antisense
5 oligonucleotide knockdown of mGluR1 alleviates both neuropathic and inflammatory pain (M.E. Fundytus *et al.*, *British Journal of Pharmacology* 132:354-367 (2001); M.E. Fundytus *et al.*, *Pharmacology, Biochemistry & Behavior* 73:401-410 (2002)). Small molecule antagonists for mGluR5-attenuated pain in *in vivo* animal models are disclosed in, e.g., K. Walker *et al.*, *Neuropharmacology* 40:1-9 (2000) and A. Dogrul *et al.*, *Neuroscience Letters*
10 292:115-118 (2000)).

Nociceptive pain has been traditionally managed by administering non-opioid analgesics, such as acetylsalicylic acid, choline magnesium trisalicylate, acetaminophen, ibuprofen, fenoprofen, diflusal, and naproxen; or opioid analgesics, including morphine, hydromorphone, methadone, levorphanol, fentanyl, oxycodone, and oxymorphone. *Id.* In
15 addition to the above-listed treatments, neuropathic pain, which can be difficult to treat, has also been treated with anti-epileptics (e.g. gabapentin, carbamazepine, valproic acid, topiramate, phenytoin), NMDA antagonists (e.g. ketamine, dextromethorphan), topical lidocaine (for post-herpetic neuralgia), and tricyclic antidepressants (e.g. fluoxetine, sertraline and amitriptyline).

20 UI is uncontrollable urination, generally caused by bladder-detrusor-muscle instability. UI affects people of all ages and levels of physical health, both in health care settings and in the community at large. At present, UI afflicts 15-30% of elderly people living at home, one-third of those living in acute-care settings, and at least one-half of those living in long-term care institutions (R.M. Resnick, *Lancet* 346:94 (1995)). Persons having
25 UI are predisposed to also having urinary-tract infections, pressure ulcers, perineal rashes and urosepsis. Psychosocially, UI is associated with embarrassment, social stigmatization, depression and a risk of institutionalization (Herzo *et al.*, *Annu. Rev. Gerontol. Geriatr.* 9:74 (1989)). Economically, the costs of UI are great; in the United States alone, health-care costs associated with UI are over \$15 billion per annum.

30 Physiologic bladder contraction results in large part from acetylcholine-induced stimulation of post-ganglionic muscarinic-receptor sites on bladder smooth muscle.

Treatments for UI include the administration of drugs having bladder-relaxant properties, which help to control bladder-detrusor-muscle overactivity. For example, anticholinergics such as propantheline bromide and glycopyrrolate, and combinations of smooth-muscle relaxants such as a combination of racemic oxybutynin and dicyclomine or an anticholinergic, have been used to treat UI (See, e.g., A.J. Wein, *Urol. Clin. N. Am.* 22:557-577 (1995); Levin *et al.*, *J. Urol.* 128:396-398 (1982); Cooke *et al.*, *S. Afr. Med. J.* 63:3 (1983); R.K. Mirakhor *et al.*, *Anaesthesia* 38:1195-1204 (1983)). These drugs are not effective, however, in all patients having uninhibited bladder contractions. Administration of anticholinergic medications represent the mainstay of this type of treatment.

None of the existing commercial drug treatments for UI, however, has achieved complete success in all classes of UI patients, nor has treatment occurred without significant adverse side effects. For example, drowsiness, dry mouth, constipation, blurred vision, headaches, tachycardia, and cardiac arrhythmia, which are related to the anticholinergic activity of traditional anti-UI drugs, can occur frequently and adversely affect patient compliance. Yet despite the prevalence of unwanted anticholinergic effects in many patients, anticholinergic drugs are currently prescribed for patients having UI. *The Merck Manual of Medical Information* 631-634 (R. Berkow ed., 1997).

Ulcers are sores occurring where the lining of the digestive tract has been eroded by stomach acids or digestive juices. The sores are typically well-defined round or oval lesions primarily occurring in the stomach and duodenum. About 1 in 10 people develop an ulcer. Ulcers develop as a result of an imbalance between acid-secretory factors, also known as “aggressive factors,” such as stomach acid, pepsin, and *Helicobacter pylori* infection, and local mucosal-protective factors, such as secretion of bicarbonate, mucus, and prostaglandins.

Treatment of ulcers typically involves reducing or inhibiting the aggressive factors. For example, antacids such as aluminum hydroxide, magnesium hydroxide, sodium bicarbonate, and calcium bicarbonate can be used to neutralize stomach acids. Antacids, however, can cause alkalosis, leading to nausea, headache, and weakness. Antacids can also interfere with the absorption of other drugs into the blood stream and cause diarrhea.

H₂ antagonists, such as cimetidine, ranitidine, famotidine, and nizatidine, are also used to treat ulcers. H₂ antagonists promote ulcer healing by reducing gastric acid and

digestive-enzyme secretion elicited by histamine and other H_2 agonists in the stomach and duodenum. H_2 antagonists, however, can cause breast enlargement and impotence in men, mental changes (especially in the elderly), headache, dizziness, nausea, myalgia, diarrhea, rash, and fever.

5 H^+ , K^+ - ATPase inhibitors such as omeprazole and lansoprazole are also used to treat ulcers. H^+ , K^+ - ATPase inhibitors inhibit the production of enzymes used by the stomach to secrete acid. Side effects associated with H^+ , K^+ - ATPase inhibitors include nausea, diarrhea, abdominal colic, headache, dizziness, somnolence, skin rashes, and transient elevations of plasma activities of aminotransferases.

10 Sucraflate is also used to treat ulcers. Sucraflate adheres to epithelial cells and is believed to form a protective coating at the base of an ulcer to promote healing. Sucraflate, however, can cause constipation, dry mouth, and interfere with the absorption of other drugs.

 Antibiotics are used when *Helicobacter pylori* is the underlying cause of the ulcer. Often antibiotic therapy is coupled with the administration of bismuth compounds
15 such as bismuth subsalicylate and colloidal bismuth citrate. The bismuth compounds are believed to enhance secretion of mucous and HCO_3^- , inhibit pepsin activity, and act as an antibacterial against *H. pylori*. Ingestion of bismuth compounds, however, can lead to elevated plasma concentrations of Bi^{+3} and can interfere with the absorption of other drugs.

 Prostaglandin analogues, such as misoprostal, inhibit secretion of acid and
20 stimulate the secretion of mucous and bicarbonate and are also used to treat ulcers, especially ulcers in patients who require nonsteroidal anti-inflammatory drugs. Effective oral doses of prostaglandin analogues, however, can cause diarrhea and abdominal cramping. In addition, some prostaglandin analogues are abortifacients.

 Carbenoxolone, a mineral corticoid, can also be used to treat ulcers.
25 Carbenoxolone appears to alter the composition and quantity of mucous, thereby enhancing the mucosal barrier. Carbenoxolone, however, can lead to Na^+ and fluid retention, hypertension, hypokalemia, and impaired glucose tolerance.

 Muscarinic cholinergic antagonists such as pirenzapine and telenzapine can also be used to reduce acid secretion and treat ulcers. Side effects of muscarinic cholinergic
30 antagonists include dry mouth, blurred vision, and constipation. *The Merck Manual of Medical Information* 496-500 (R. Berkow ed., 1997) and *Goodman and Gilman's The*

Pharmacological Basis of Therapeutics 901-915 (J. Hardman and L. Limbird eds., 9th ed. 1996).

IBD is a chronic disorder in which the bowel becomes inflamed, often causing recurring abdominal cramps and diarrhea. The two types of IBD are Crohn's disease and
5 ulcerative colitis.

Crohn's disease, which can include regional enteritis, granulomatous ileitis, and ileocolitis, is a chronic inflammation of the intestinal wall. Crohn's disease occurs equally in both sexes and is more common in Jews of eastern-European ancestry. Most cases of Crohn's disease begin before age 30 and the majority start between the ages of 14 and 24.
10 The disease typically affects the full thickness of the intestinal wall. Generally the disease affects the lowest portion of the small intestine (ileum) and the large intestine, but can occur in any part of the digestive tract.

Early symptoms of Crohn's disease are chronic diarrhea, crampy abdominal pain, fever, loss of appetite, and weight loss. Complications associated with Crohn's disease
15 include the development of intestinal obstructions, abnormal connecting channels (fistulas), and abscesses. The risk of cancer of the large intestine is increased in people who have Crohn's disease. Often Crohn's disease is associated with other disorders such as gallstones, inadequate absorption of nutrients, amyloidosis, arthritis, episcleritis, aphthous stomatitis, erythema nodosum, pyoderma gangrenosum, ankylosing spondylitis, sacroilitis, uveitis, and
20 primary sclerosing cholangitis. There is no known cure for Crohn's disease.

Cramps and diarrhea, side effects associated with Crohn's disease, can be relieved by anticholinergic drugs, diphenoxylate, loperamide, deodorized opium tincture, or codeine. Generally, the drug is taken orally before a meal.

Broad-spectrum antibiotics are often administered to treat the symptoms of
25 Crohn's disease. The antibiotic metronidazole is often administered when the disease affects the large intestine or causes abscesses and fistulas around the anus. Long-term use of metronidazole, however, can damage nerves, resulting in pins-and-needles sensations in the arms and legs. Sulfasalazine and chemically related drugs can suppress mild inflammation, especially in the large intestine. These drugs, however, are less effective in sudden, severe
30 flare-ups. Corticosteroids, such as prednisone, reduce fever and diarrhea and relieve abdominal pain and tenderness. Long-term corticosteroid therapy, however, invariably results

in serious side effects such as high blood-sugar levels, increased risk of infection, osteoporosis, water retention, and fragility of the skin. Drugs such as azathioprine and mercaptopurine can compromise the immune system and are often effective for Crohn's disease in patients that do not respond to other drugs. These drugs, however, usually need 3 to 6 months before they produce benefits and can cause serious side effects such as allergy, pancreatitis, and low white-blood-cell count.

When Crohn's disease causes the intestine to be obstructed or when abscesses or fistulas do not heal, surgery can be necessary to remove diseased sections of the intestine. Surgery, however, does not cure the disease, and inflammation tends to recur where the intestine is rejoined. In almost half of the cases a second operation is needed. *The Merck Manual of Medical Information* 528-530 (R. Berkow ed., 1997).

Ulcerative colitis is a chronic disease in which the large intestine becomes inflamed and ulcerated, leading to episodes of bloody diarrhea, abdominal cramps, and fever. Ulcerative colitis usually begins between ages 15 and 30; however, a small group of people have their first attack between ages 50 and 70. Unlike Crohn's disease, ulcerative colitis never affects the small intestine and does not affect the full thickness of the intestine. The disease usually begins in the rectum and the sigmoid colon and eventually spreads partially or completely through out the large intestine. The cause of ulcerative colitis is unknown.

Treatment of ulcerative colitis is directed to controlling inflammation, reducing symptoms, and replacing lost fluids and nutrients. Anticholinergic drugs and low doses of diphenoxylate or loperamide are administered for treating mild diarrhea. For more intense diarrhea higher doses of diphenoxylate or loperamide, or deodorized opium tincture or codeine are administered. Sulfasalazine, olsalazine, prednisone, or mesalamine can be used to reduce inflammation. Azathioprine and mercaptopurine have been used to maintain remissions in ulcerative-colitis patients who would otherwise need long-term corticosteroid treatment. In severe cases of ulcerative colitis the patient is hospitalized and given corticosteroids intravenously. People with severe rectal bleeding can require transfusions and intravenous fluids. If toxic colitis develops and treatments fail, surgery to remove the large intestine can be necessary. Non-emergency surgery can be performed if cancer is diagnosed, precancerous lesions are detected, or unremitting chronic disease would otherwise make the person an invalid or dependent on high doses of corticosteroids. Complete removal of the

large intestine and rectum permanently cures ulcerative colitis. *The Merck Manual of Medical Information* 530-532 (R. Berkow ed., 1997) and *Goodman and Gilman's The Pharmacological Basis of Therapeutics* (J. Hardman and L. Limbird eds., 9th ed. 1996).

IBS is a disorder of motility of the entire gastrointestinal tract, causing
5 abdominal pain, constipation, and/or diarrhea. IBS affects three-times more women than men. In IBS stimuli such as stress, diet, drugs, hormones, or irritants can cause the gastrointestinal tract to contract abnormally. During an episode of IBS contractions of the gastrointestinal tract become stronger and more frequent, resulting in the rapid transit of food and feces through the small intestine, often leading to diarrhea. Cramps result from the
10 strong contractions of the large intestine and increased sensitivity of pain receptors in the large intestine.

There are two major types of IBS. The first type, spastic-colon type, is commonly triggered by eating, and usually produces periodic constipation and diarrhea with pain. Mucous often appears in the stool. The pain can come in bouts of continuous dull
15 aching pain or cramps, usually in the lower abdomen. The person suffering from spastic-colon type IBS can also experience bloating, gas, nausea, headache, fatigue, depression, anxiety, and difficulty concentrating. The second type of IBS usually produces painless diarrhea or constipation. The diarrhea can begin suddenly and with extreme urgency. Often the diarrhea occurs soon after a meal and can sometimes occur immediately upon awakening.

20 Treatment of IBS typically involves modification of an IBS-patient's diet. Often it is recommended that an IBS patient avoid beans, cabbage, sorbitol, and fructose. A low-fat, high-fiber diet can also help some IBS patients. Regular physical activity can also help keep the gastrointestinal tract functioning properly. Drugs such as propantheline that slow the function of the gastrointestinal tract are generally not effective for treating IBS.
25 Antidiarrheal drugs, such as diphenoxylate and loperamide, help with diarrhea. *The Merck Manual of Medical Information* 525-526 (R. Berkow ed., 1997).

Many drugs can cause physical and/or psychological addiction. Those most well known types of these drugs include opiates, such as heroin, opium, and morphine; sympathomimetics, including cocaine and amphetamines; sedative-hypnotics, including
30 alcohol, benzodiazepines and barbiturates; and nicotine, which has effects similar to opioids and sympathomimetics. Drug addiction is characterized by a craving or compulsion for

taking the drug and an inability to limit its intake. Additionally, drug dependence is associated with drug tolerance, the loss of effect of the drug following repeated administration, and withdrawal, the appearance of physical and behavioral symptoms when the drug is not consumed. Sensitization occurs if repeated administration of a drug leads to an increased response to each dose. Tolerance, sensitization, and withdrawal are phenomena evidencing a change in the central nervous system resulting from continued use of the drug. This change can motivate the addicted individual to continue consuming the drug despite serious social, legal, physical and/or professional consequences. (See, e.g., U.S. Patent No. 6,109,269 to Rise *et al.*).

10 Certain pharmaceutical agents have been administered for treating addiction. U.S. Patent No. 5,556,838 to Mayer *et al.* discloses the use of nontoxic NMDA-blocking agents co-administered with an addictive substance to prevent the development of tolerance or withdrawal symptoms. U.S. Patent No. 5,574,052 to Rose *et al.* discloses co-administration of an addictive substance with an antagonist to partially block the
15 pharmacological effects of the substance. U.S. Patent No. 5,075,341 to Mendelson *et al.* discloses the use of a mixed opiate agonist/antagonist to treat cocaine and opiate addiction. U.S. Patent No. 5,232,934 to Downs discloses administration of 3-phenoxypropidine to treat addiction. U.S. Patents No. 5,039,680 and 5,198,459 to Imperato *et al.* disclose using a serotonin antagonist to treat chemical addiction. U.S. Patent No. 5,556,837 to Nestler *et al.*
20 discloses infusing BDNF or NT-4 growth factors to inhibit or reverse neurological adaptive changes that correlate with behavioral changes in an addicted individual. U.S. Patent No. 5,762,925 to Sagan discloses implanting encapsulated adrenal medullary cells into an animal's central nervous system to inhibit the development of opioid intolerance. U.S. Patent No. 6,204,284 to Beer *et al.* discloses racemic (\pm)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane for use in the prevention or relief of a withdrawal syndrome resulting
25 from addiction to drugs and for the treatment of chemical dependencies.

 Parkinson's disease is a clinical syndrome comprising bradykinesia (slowness and poverty of movement), muscular rigidity, resting tremor (which usually abates during voluntary movement), and an impairment of postural balance leading to disturbance of gait
30 and falling. The features of Parkinson's disease are a loss of pigmented, dopaminergic neurons of the substantia nigra pars compacta and the appearance of intracellular inclusions

known as Lewy bodies (*Goodman and Gillman's The Pharmaceutical Basis of Therapeutics* 506 (9th ed. 1996)). Without treatment, Parkinson's disease progresses to a rigid akinetic state in which patients are incapable of caring for themselves. Death frequently results from complications of immobility, including aspiration pneumonia or pulmonary embolism. Drugs
5 commonly used for the treatment of Parkinson's disease include carbidopa/levodopa, pergolide, bromocriptine, selegiline, amantadine, and trihexyphenidyl hydrochloride. There remains, however, a need for drugs useful for the treatment of Parkinson's disease and having an improved therapeutic profile.

Anxiety is a fear, apprehension, or dread of impending danger often
10 accompanied by restlessness, tension, tachycardia, and dyspnea. Other symptoms commonly associated with anxiety include depression, especially accompanied with dysthymic disorder (chronic "neurotic" depression); panic disorder; agoraphobia and other specific phobias; eating disorders; and many personality disorders. Often anxiety is unattached to a clearly identified treatable primary illness. If a primary illness is found, however, it can be desirable
15 to deal with the anxiety at the same time as the primary illness.

Currently, benzodiazepines are the most commonly used anti-anxiety agents for generalized anxiety disorder. Benzodiazepines, however, carry the risk of producing impairment of cognition and skilled motor functions, particularly in the elderly, which can result in confusion, delirium, and falls with fractures. Sedatives are also commonly
20 prescribed for treating anxiety. The azapirones, such as buspirone, are also used to treat moderate anxiety. The azapirones, however, are less useful for treating severe anxiety accompanied with panic attacks.

Epilepsy is a disorder characterized by the tendency to have recurring seizures. The etiology commonly consists of lesions in some part of the cortex, such as a tumor;
25 developmental malformation; or damage due to trauma or stroke. In some cases the etiology is genetic. An epileptic seizure can be triggered by repetitive sounds, flashing lights, video games, or touching certain parts of the body. Epilepsy is typically treated with anti-seizure drugs. In epilepsy cases, where anti-seizure drugs are ineffective, and the defect in the brain is isolated to a small area of the brain, surgical removal of that part of the brain can be helpful
30 in alleviating the seizures. In patients who have several sources for the seizures or who have

seizures that spread quickly to all parts of the brain, surgical removal of the nerve fibers that connect the two sides of the brain can be helpful.

Examples of drugs for treating a seizure and epilepsy include carbamazepine, ethosuximide, gabapentin, lamotrigine, phenobarbital, phenytoin, primidone, valproic acid, 5 trimethadione, benzodiazepines, γ -vinyl GABA, acetazolamide, and felbamate. Anti-seizure drugs, however, can have side effects such as drowsiness; hyperactivity; hallucinations; inability to concentrate; central and peripheral nervous system toxicity, such as nystagmus, ataxia, diplopia, and vertigo; gingival hyperplasia; gastrointestinal disturbances such as nausea, vomiting, epigastric pain, and anorexia; endocrine effects such as inhibition of 10 antidiuretic hormone, hyperglycemia, glycosuria, osteomalacia; and hypersensitivity such as scarlatiniform rash, morbilliform rash, Stevens-Johnson syndrome, systemic lupus erythematosus, and hepatic necrosis; and hematological reactions such as red-cell aplasia, agranulocytosis, thrombocytopenia, aplastic anemia, and megaloblastic anemia. *The Merck Manual of Medical Information* 345-350 (R. Berkow ed., 1997).

15 A seizure is the result of abnormal electrical discharge in the brain. The discharge can involve a small area of the brain and lead to the person only noticing an odd taste or smell or it can involve a large area of the brain and lead to convulsions, *i.e.*, a seizure that causes jerking and spasms of the muscles throughout the body. Convulsions can also result in brief attacks of altered consciousness and loss of consciousness, muscle control, or 20 bladder control. A seizure is often preceded by auras, *i.e.*, unusual sensations of smell, taste, or vision or an intense feeling that a seizure is about to begin. A seizure typically lasts for about 2 to 5 minutes. When the seizure ends the person can have headache, sore muscles, unusual sensations, confusion, and profound fatigue (postictal state). Usually the person cannot remember what happened during the seizure.

25 A stroke or cerebrovascular accident, is the death of brain tissue (cerebral infarction) resulting from the lack of blood flow and insufficient oxygen to the brain. A stroke can be either ischemic or hemorrhagic. In an ischemic stroke, blood supply to the brain is cut off because of atherosclerosis or a blood clot that has blocked a blood vessel. In a hemorrhagic stroke, a blood vessel bursts preventing normal blood flow and allowing blood 30 to leak into an area of the brain and destroying it. Most strokes develop rapidly and cause brain damage within minutes. In some cases, however, strokes can continue to worsen for

several hours or days. Symptoms of strokes vary depending on what part of the brain is effected. Symptoms include loss or abnormal sensations in an arm or leg or one side of the body, weakness or paralysis of an arm or leg or one side of the body, partial loss of vision or hearing, double vision, dizziness, slurred speech, difficulty in thinking of the appropriate word or saying it, inability to recognize parts of the body, unusual movements, loss of bladder control, imbalance, and falling, and fainting. The symptoms can be permanent and can be associated with coma or stupor. Strokes can cause edema or swelling of the brain which can further damage brain tissue. For persons suffering from a stroke, intensive rehabilitation can help overcome the disability caused by impairment of brain tissue. Rehabilitation trains other parts of the brain to assume the tasks previously performed by the damaged part.

Examples of drugs for treating strokes include anticoagulants such as heparin, drugs that break up clots such as streptokinase or tissue plasminogen activator, and drugs that reduce swelling such as mannitol or corticosteroids. *The Merck Manual of Medical Information* 352-355 (R. Berkow ed., 1997).

Pruritus is an unpleasant sensation that prompts scratching. Pruritus can be attributed to dry skin, scabies, dermatitis, herpetiformis, atopic dermatitis, *pruritus vulvae et ani*, miliaria, insect bites, pediculosis, contact dermatitis, drug reactions, urticaria, urticarial eruptions of pregnancy, psoriasis, lichen planus, lichen simplex chronicus, exfoliative dermatitis, folliculitis, bullous pemphigoid, and fiberglass dermatitis. Conventionally, pruritus is treated by phototherapy with ultraviolet B or PUVA or with therapeutic agents such as naltrexone, nalmefene, danazol, tricyclics, and antidepressants.

Selective antagonists of the metabotropic glutamate receptor 5 (“mGluR5”) have been shown to exert analgesic activity in *in vivo* animal models (K. Walker *et al.*, *Neuropharmacology* 40:1-9 (2000) and A. Dogrul *et al.*, *Neuroscience Letters*, 292(2):115-118 (2000)).

Selective antagonists of the mGluR5 receptor have also been shown to exert anxiolytic and anti-depressant activity in *in vivo* animal models (E. Tatarczynska *et al.*, *Br. J. Pharmacol.* 132(7):1423-1430 (2001) and P.J.M. Will *et al.*, *Trends in Pharmacological Sciences* 22(7):331-37 (2001)).

Selective antagonists of the mGluR5 receptor have also been shown to exert anti-Parkinson activity *in vivo* (K. J. Ossowska *et al.*, *Neuropharmacology* 41(4):413-20 (2001) and P.J.M. Will *et al.*, *Trends in Pharmacological Sciences* 22(7):331-37 (2001)).

Selective antagonists of the mGluR5 receptor have also been shown to exert
5 anti-dependence activity *in vivo* (C. Chiamulera *et al.*, *Nature Neuroscience* 4(9):873-74 (2001)).

International publication no. WO 02/16318 discloses a class of N-cyanoimines allegedly useful for treating a acute pain, urinary bladder hypersensitiveness, an ulcer, IBD, and IBS.

10 There remains, however, a clear need in the art for new drugs useful for treating or preventing pain, UI, an ulcer, IBD, IBS, an addictive disorder, Parkinson's disease, parkinsonism, anxiety, epilepsy, stroke, a seizure, a pruritic condition, psychosis, a cognitive disorder, a memory deficit, restricted brain function, Huntington's chorea, ALS, dementia, retinopathy, a muscle spasm, a migraine, vomiting, dyskinesia, or depression.

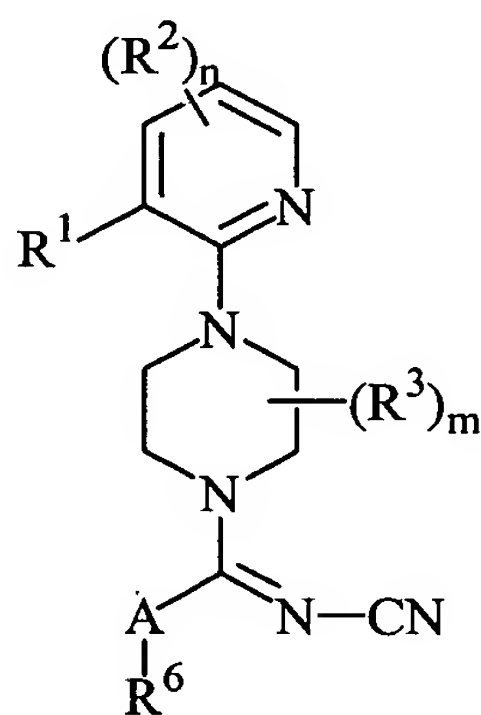
15 Citation of any reference in Section 2 of this application is not to be construed as an admission that such reference is prior art to the present application

3. SUMMARY OF THE INVENTION

The present invention encompasses compounds having the formula (I):

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(I)

and pharmaceutically acceptable salts thereof, wherein:

30

A is -NR⁴-, -O-, or -S-;

R¹ is -halo, -CH₃, -NO₂, -CN, -OH, -OCH₃, -NH₂, -C(halo)₃, -CH(halo)₂, or

-CH₂(halo);

each R² is independently:

(a) -halo, -CN, -OH, -NO₂, or -NH₂;

5 (b) -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(C₃-C₇)heterocycle, or -(C₇-C₁₀)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R⁵ groups; or

10 (c) -phenyl, -naphthyl, -(C₁₄)aryl, or -(C₅-C₁₀)heteroaryl, each of which is unsubstituted or substituted with one or more R⁷ groups;

each R³ is independently:

(a) -halo, -CN, -OH, -NO₂, or -NH₂; or

15 (b) -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(C₃-C₇)heterocycle, or -(C₇-C₁₀)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R⁵ groups; or

(c) -phenyl, -naphthyl, -(C₁₄)aryl or -(C₅-C₁₀)heteroaryl, each of which is unsubstituted or substituted with one or more R⁷ groups;

20 R⁴ is -(C₁-C₆)alkyl, or -O-(C₁-C₆)alkyl;

each R⁵ is independently -CN, -OH, -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -halo, -N₃, -NO₂, -N(R⁸)₂, -CH=NR⁸, -NR⁸OH, -OR⁸, -COR⁸, -C(O)OR⁸, -OC(O)R⁸, -OC(O)OR⁸, -SR⁸, -S(O)R⁸, or -S(O)₂R⁸;

R⁶ is -phenyl, -naphthyl, -(C₃-C₈)cycloalkyl, -(C₁₄)aryl, or -(C₅-C₁₀)heteroaryl,

25 each of which is unsubstituted or substituted with one or more R⁷ groups;

each R⁷ is independently -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₃-C₈)cycloalkyl, -(C₅-C₈)cycloalkenyl, -phenyl, -(C₃-C₅)heterocycle, -C(halo)₃, -CH₂(halo), -CH(halo)₂, -CN, -OH, -halo, -N₃, -NO₂, -N(R⁸)₂, -CH=NR⁸, -NR⁸OH, -OR⁸, -COR⁸, -C(O)OR⁸, -OC(O)R⁸, -OC(O)OR⁸, -SR⁸, -S(O)R⁸, or -S(O)₂R⁸;

30 each R⁸ is independently -H, -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₃-C₈)cycloalkyl, -(C₅-C₈)cycloalkenyl, -phenyl, -(C₃-C₅)heterocycle, -C(halo)₃,

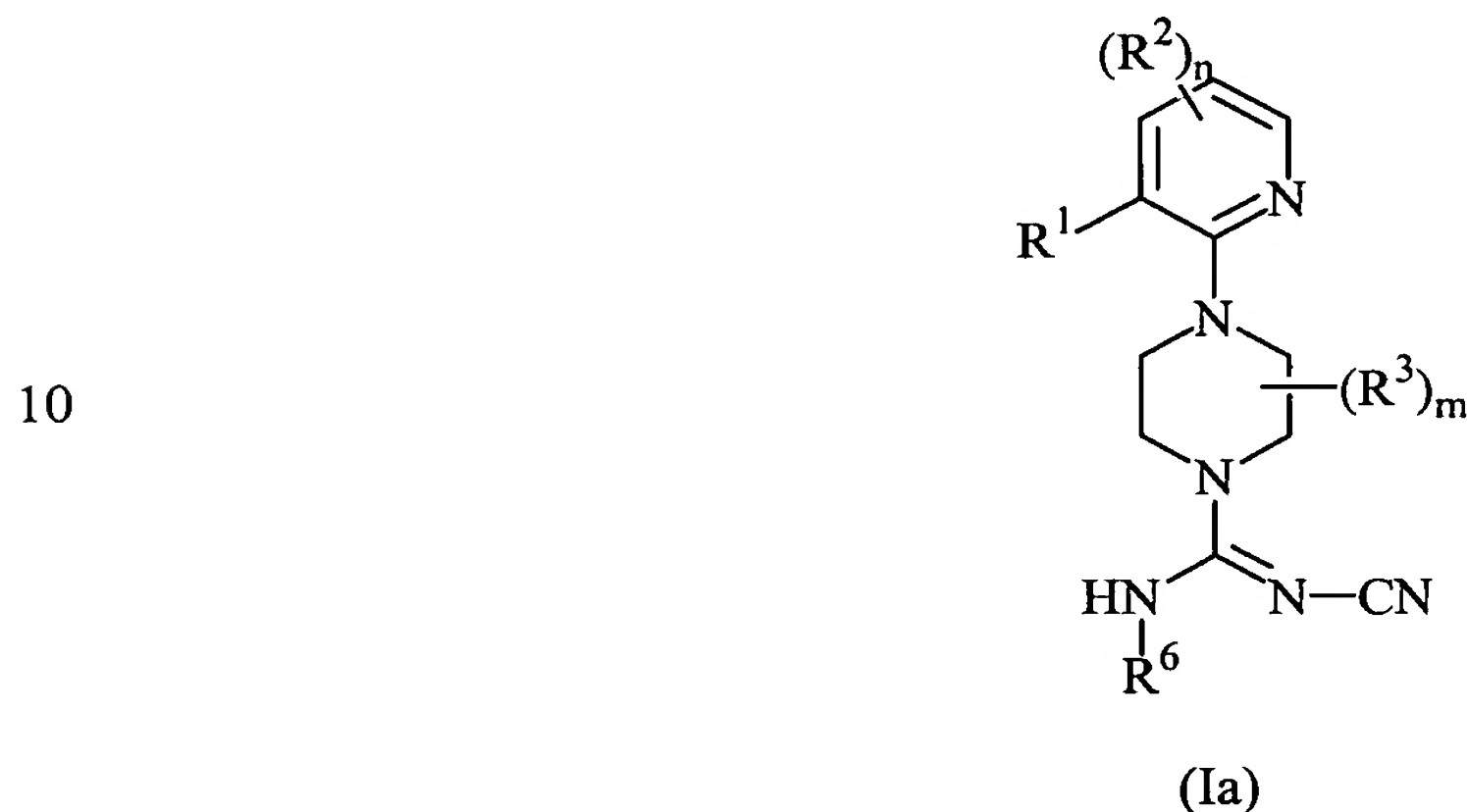
-CH₂(halo), or -CH(halo)₂;

each halo is independently -F, -Cl, -Br or -I;

n is an integer ranging from 0 to 3; and

m is an integer ranging from 0 to 2.

5 The present invention encompasses compounds having the formula (Ia):



15 and pharmaceutically acceptable salts thereof, wherein:

R¹ is -halo, -CH₃, -NO₂, -CN, -OH, -OCH₃, -NH₂, -C(halo)₃, -CH(halo)₂, or -CH₂(halo);

each R² is independently:

- 20 (a) -halo, -CN, -OH, -NO₂, or -NH₂;
- (b) -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(C₃-C₇)heterocycle, or -(C₇-C₁₀)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R⁵ groups; or
- 25 (c) -phenyl, -naphthyl, -(C₁₄)aryl, or -(C₅-C₁₀)heteroaryl, each of which is unsubstituted or substituted with one or more R⁷ groups;

each R³ is independently:

- (a) -halo, -CN, -OH, -NO₂, or -NH₂; or
- 30 (b) -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(C₃-

C₇)heterocycle, or -(C₇-C₁₀)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R⁵ groups; or

(c) -phenyl, -naphthyl, -(C₁₄)aryl or -(C₅-C₁₀)heteroaryl, each of which is unsubstituted or substituted with one or more R⁷ groups;

5 each R⁵ is independently -CN, -OH, -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkenyl, -halo, -N₃, -NO₂, -N(R⁸)₂, -CH=NR⁸, -NR⁸OH, -OR⁸, -COR⁸, -C(O)OR⁸, -OC(O)R⁸, -OC(O)OR⁸, -SR⁸, -S(O)R⁸, or -S(O)₂R⁸;

R⁶ is:

10 (a) -naphthyl, -(C₁₄)aryl, or -(C₃-C₈)cycloalkyl each of which is unsubstituted or substituted with one or more R⁷ groups; or

(b) pyridyl, furyl, benzofuranyl, thiophenyl, benzothiophenyl, quinolinyl, indolyl, oxazolyl, benzoxazolyl, imidazolyl, benzimidazolyl, thiazolyl, benzothiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiadiazolyl, triazinyl, cinnolinyl, phthalazinyl, or
15 quinazolinyl, each of which is substituted with one or more R⁷ groups;

each R⁷ is independently -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₃-C₈)cycloalkyl, -(C₅-C₈)cycloalkenyl, -phenyl, -(C₃-C₅)heterocycle, -C(halo)₃, -CH₂(halo), -CH(halo)₂, -CN, -OH, -halo, -N₃, -NO₂, -N(R⁸)₂, -CH=NR⁸, -NR⁸OH, -OR⁸, -COR⁸, -C(O)OR⁸, -OC(O)R⁸, -OC(O)OR⁸, -SR⁸, -S(O)R⁸, or -S(O)₂R⁸;

20 each R⁸ is independently -H, -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₃-C₈)cycloalkyl, -(C₅-C₈)cycloalkenyl, -phenyl, -(C₃-C₅)heterocycle, -C(halo)₃, -CH₂(halo), or -CH(halo)₂;

each halo is independently -F, -Cl, -Br or -I;

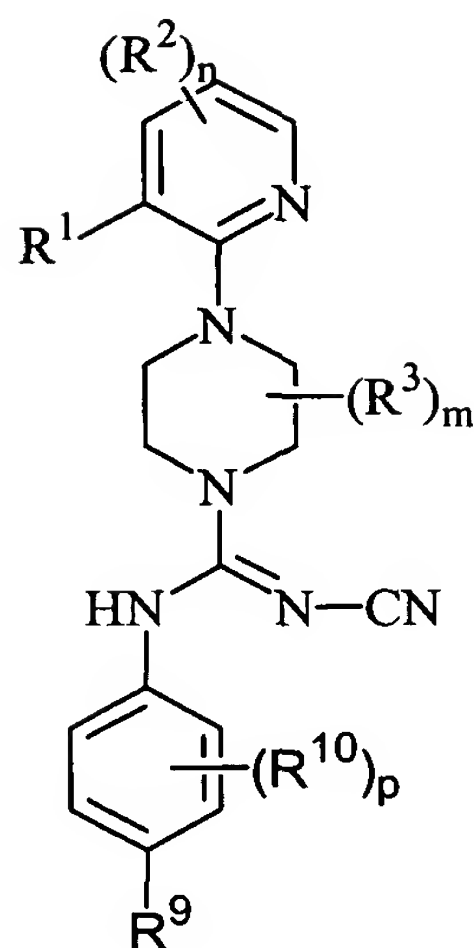
n is an integer ranging from 0 to 3; and

25 m is an integer ranging from 0 to 2.

The present invention encompasses compounds having the formula (Ib):

5

10



(Ib)

and pharmaceutically acceptable salts thereof, wherein:

R¹ is -halo, -CH₃, -NO₂, -CN, -OH, -OCH₃, -NH₂, -C(halo)₃, -CH(halo)₂, or
15 -CH₂(halo);

each R² is independently:

(a) -halo, -CN, -OH, -NO₂, or -NH₂;
 (b) -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-
 C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-
 20 C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(C₃-
 C₇)heterocycle, or -(C₇-C₁₀)bicycloheterocycle, each of which is unsubstituted
 or substituted with one or more R⁵ groups; or

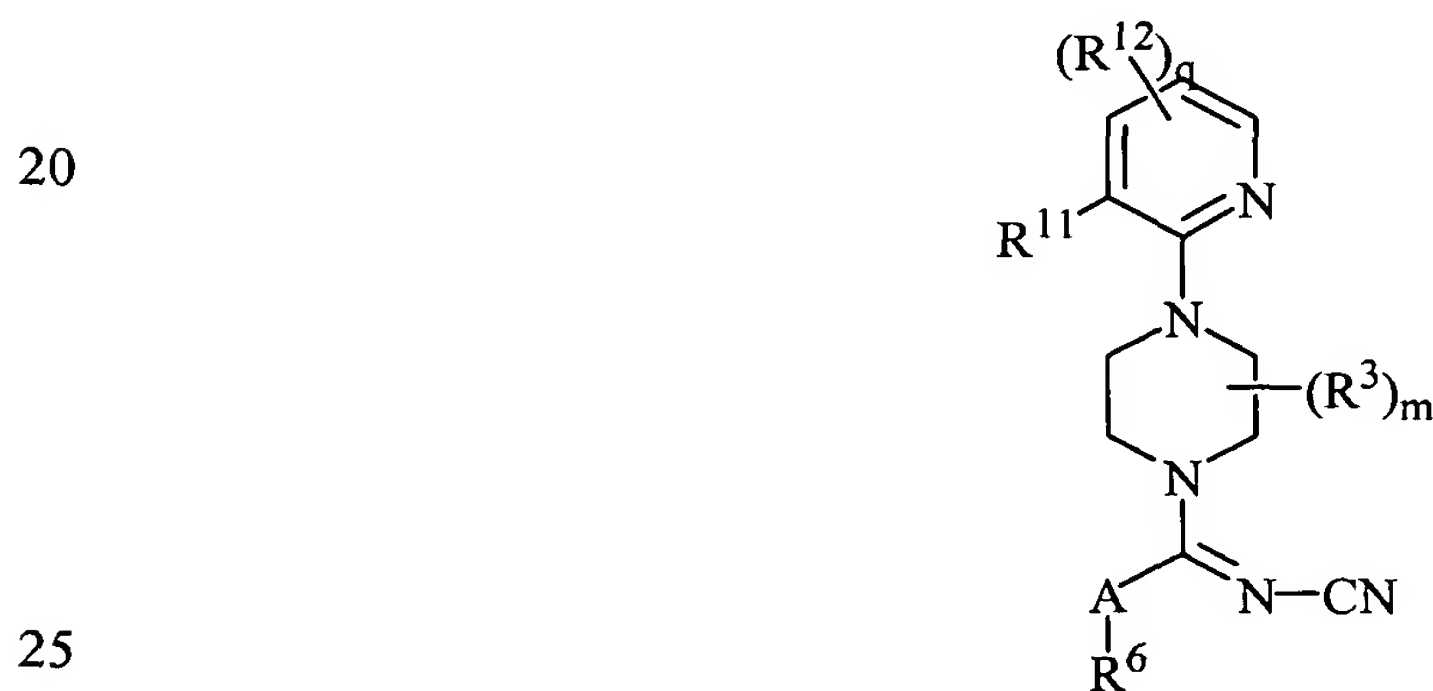
(c) -phenyl, -naphthyl, -(C₁₄)aryl, or -(C₅-C₁₀)heteroaryl, each of
 which is unsubstituted or substituted with one or more R⁷ groups;

25 each R³ is independently:

(a) -halo, -CN, -OH, -NO₂, or -NH₂; or
 (b) -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-
 C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-
 C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(C₃-
 30 C₇)heterocycle, or -(C₇-C₁₀)bicycloheterocycle, each of which is unsubstituted
 or substituted with one or more R⁵ groups; or

(c) -phenyl, -naphthyl, $-(C_{14})$ aryl or $-(C_5-C_{10})$ heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups;
 each R^5 is independently -CN, -OH, $-(C_1-C_6)$ alkyl, $-(C_2-C_6)$ alkenyl, -
 (C_2-C_6) alkynyl, -halo, $-N_3$, $-NO_2$, $-N(R^8)_2$, $-CH=NR^8$, $-NR^8OH$, $-OR^8$, $-COR^8$, $-C(O)OR^8$,
 5 $-OC(O)R^8$, $-OC(O)OR^8$, $-SR^8$, $-S(O)R^8$, or $-S(O)_2R^8$;
 each R^7 , R^9 , and R^{10} is independently $-(C_1-C_6)$ alkyl, $-(C_2-C_6)$ alkenyl, -
 (C_2-C_6) alkynyl, $-(C_3-C_8)$ cycloalkyl, $-(C_5-C_8)$ cycloalkenyl, -phenyl, $-(C_3-C_5)$ heterocycle, -
 $C(halo)_3$, $-CH(halo)_2$, $-CH_2(halo)$, -CN, -OH, -halo, $-N_3$, $-NO_2$, $-N(R^8)_2$, $-CH=NR^8$, $-NR^8OH$,
 $-OR^8$, $-COR^8$, $-C(O)OR^8$, $-OC(O)R^8$, $-OC(O)OR^8$, $-SR^8$, $-S(O)R^8$, or $-S(O)_2R^8$;
 10 each R^8 is independently -H, $-(C_1-C_6)$ alkyl, $-(C_2-C_6)$ alkenyl, $-(C_2-C_6)$ alkynyl,
 $-(C_3-C_8)$ cycloalkyl, $-(C_5-C_8)$ cycloalkenyl, -phenyl, $-(C_3-C_5)$ heterocycle, $-C(halo)_3$,
 $-CH_2(halo)$, or $-CH(halo)_2$;
 each halo is independently -F, -Cl, -Br or -I;
 n is an integer ranging from 0 to 3;
 15 m is an integer ranging from 0 to 2; and
 p is an integer ranging from 0 to 4.

The present invention encompasses compounds having the formula (Ic):



(Ic)

and pharmaceutically acceptable salts thereof, wherein:

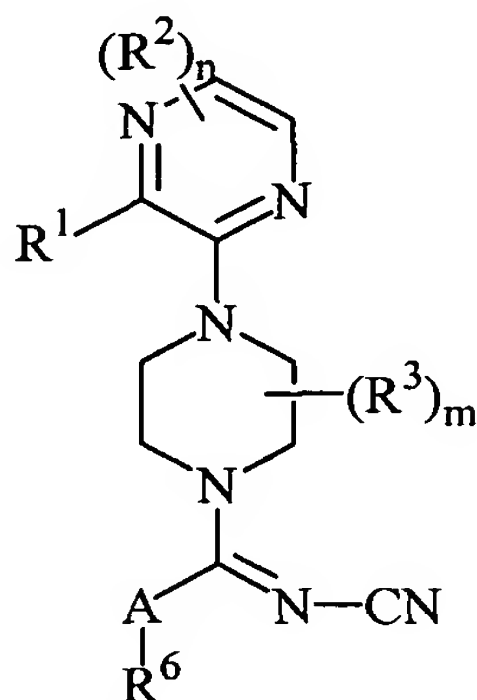
A is $-NR^4-$, $-O-$, or $-S-$;
 30 each R^3 is independently:
 (a) -halo, -CN, -OH, $-NO_2$, or $-NH_2$; or

- (b) $-(C_1-C_{10})$ alkyl, $-(C_2-C_{10})$ alkenyl, $-(C_2-C_{10})$ alkynyl, $-(C_3-C_{10})$ cycloalkyl, $-(C_8-C_{14})$ bicycloalkyl, $-(C_8-C_{14})$ tricycloalkyl, $-(C_5-C_{10})$ cycloalkenyl, $-(C_8-C_{14})$ bicycloalkenyl, $-(C_8-C_{14})$ tricycloalkenyl, $-(C_3-C_7)$ heterocycle, or $-(C_7-C_{10})$ bicycloheterocycle, each of which is unsubstituted or substituted with one or more R^5 groups; or
- (c) -phenyl, -naphthyl, $-(C_{14})$ aryl or $-(C_5-C_{10})$ heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups;
- R^4 is $-(C_1-C_6)$ alkyl, or $-O-(C_1-C_6)$ alkyl;
- each R^5 is independently -CN, -OH, $-(C_1-C_6)$ alkyl, $-(C_2-C_6)$ alkenyl, $-(C_2-C_6)$ alkynyl, $-(C_2-C_6)$ alkenyl, -halo, $-N_3$, $-NO_2$, $-N(R^8)_2$, $-CH=NR^8$, $-NR^8OH$, $-OR^8$, $-COR^8$, $-C(O)OR^8$, $-OC(O)R^8$, $-OC(O)OR^8$, $-SR^8$, $-S(O)R^8$, or $-S(O)_2R^8$;
- R^6 is -phenyl, -naphthyl, $-(C_3-C_8)$ cycloalkyl, $-(C_{14})$ aryl, or $-(C_5-C_{10})$ heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups;
- each R^7 is independently $-(C_1-C_6)$ alkyl, $-(C_2-C_6)$ alkenyl, $-(C_2-C_6)$ alkynyl, $-(C_3-C_8)$ cycloalkyl, $-(C_5-C_8)$ cycloalkenyl, -phenyl, $-(C_3-C_5)$ heterocycle, $-C(halo)_3$, $-CH(halo)_2$, $-CH_2(halo)$, -CN, -OH, -halo, $-N_3$, $-NO_2$, $-N(R^8)_2$, $-CH=NR^8$, $-NR^8OH$, $-OR^8$, $-COR^8$, $-C(O)OR^8$, $-OC(O)R^8$, $-OC(O)OR^8$, $-SR^8$, $-S(O)R^8$, or $-S(O)_2R^8$;
- each R^8 is independently -H, $-(C_1-C_6)$ alkyl, $-(C_2-C_6)$ alkenyl, $-(C_2-C_6)$ alkynyl, $-(C_3-C_8)$ cycloalkyl, $-(C_5-C_8)$ cycloalkenyl, -phenyl, $-(C_3-C_5)$ heterocycle, $-C(halo)_3$, $-CH_2(halo)$, or $-CH(halo)_2$;
- R^{11} is -hydrogen, -halo, $-CH_3$, $-NO_2$, -CN, -OH, $-OCH_3$, $-NH_2$, $-C(halo)_3$, $-CH(halo)_2$, or $-CH_2(halo)$;
- each R^{12} is independently:
- (a) -halo, -CN, -OH, $-NO_2$, or $-NH_2$;
- (b) $-(C_1-C_{10})$ alkyl, $-(C_2-C_{10})$ alkenyl, $-(C_2-C_{10})$ alkynyl, $-(C_3-C_{10})$ cycloalkyl, $-(C_8-C_{14})$ bicycloalkyl, $-(C_8-C_{14})$ tricycloalkyl, $-(C_5-C_{10})$ cycloalkenyl, $-(C_8-C_{14})$ bicycloalkenyl, $-(C_8-C_{14})$ tricycloalkenyl, $-(C_3-C_7)$ heterocycle, or $-(C_7-C_{10})$ bicycloheterocycle, each of which is unsubstituted or substituted with one or more R^5 groups; or
- (c) -phenyl, -naphthyl, $-(C_{14})$ aryl, or $-(C_5-C_{10})$ heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups;

m is an integer ranging from 0 to 2; and

q is an integer ranging from 0 to 3.

The present invention also encompasses compounds having the formula (II):



(II)

and pharmaceutically acceptable salts thereof, wherein:

A is $-NR^4-$, $-O-$, or $-S-$;

15 R^1 is -halo, $-CH_3$, $-NO_2$, $-CN$, $-OH$, $-OCH_3$, $-NH_2$, $-C(halo)_3$, $-CH(halo)_2$, or $-CH_2(halo)$;

each R^2 is independently:

(a) -halo, $-CN$, $-OH$, $-NO_2$, or $-NH_2$;

20 (b) $-(C_1-C_{10})$ alkyl, $-(C_2-C_{10})$ alkenyl, $-(C_2-C_{10})$ alkynyl, $-(C_3-C_{10})$ cycloalkyl, $-(C_8-C_{14})$ bicycloalkyl, $-(C_8-C_{14})$ tricycloalkyl, $-(C_5-C_{10})$ cycloalkenyl, $-(C_8-C_{14})$ bicycloalkenyl, $-(C_8-C_{14})$ tricycloalkenyl, $-(C_3-C_7)$ heterocycle, or $-(C_7-C_{10})$ bicycloheterocycle, each of which is unsubstituted or substituted with one or more R^5 groups; or

25 (c) -phenyl, -naphthyl, $-(C_{14})$ aryl, or $-(C_5-C_{10})$ heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups;

each R^3 is independently:

(a) -halo, $-CN$, $-OH$, $-NO_2$, or $-NH_2$;

30 (b) $-(C_1-C_{10})$ alkyl, $-(C_2-C_{10})$ alkenyl, $-(C_2-C_{10})$ alkynyl, $-(C_3-C_{10})$ cycloalkyl, $-(C_8-C_{14})$ bicycloalkyl, $-(C_8-C_{14})$ tricycloalkyl, $-(C_5-C_{10})$ cycloalkenyl, $-(C_8-C_{14})$ bicycloalkenyl, $-(C_8-C_{14})$ tricycloalkenyl, $-(C_3-$

C₇)heterocycle, or -(C₇-C₁₀)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R⁵ groups; or

(c) -phenyl, -naphthyl, -(C₁₄)aryl or -(C₅-C₁₀)heteroaryl, each of which is unsubstituted or substituted with one or more R⁷ groups;

R⁴ is hydrogen, -(C₁-C₆)alkyl, or -O-(C₁-C₆)alkyl;

each R⁵ is independently -CN, -OH, -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -halo, -N₃, -NO₂, -N(R⁸)₂, -CH=NR⁸, -NR⁸OH, -OR⁸, -COR⁸, -C(O)OR⁸, -OC(O)R⁸, -OC(O)OR⁸, -SR⁸, -S(O)R⁸, or -S(O)₂R⁸;

R⁶ is -phenyl, -naphthyl, -(C₃-C₈)cycloalkyl, -(C₁₄)aryl, or -(C₅-C₁₀)heteroaryl,

each of which is unsubstituted or substituted with one or more R⁷ groups;

each R⁷ is independently -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₃-C₈)cycloalkyl, -(C₅-C₈)cycloalkenyl, -phenyl, -(C₃-C₅)heterocycle, -C(halo)₃, -CH₂(halo), -CH(halo)₂, -CN, -OH, -halo, -N₃, -NO₂, -N(R⁸)₂, -CH=NR⁸, -NR⁸OH, -OR⁸, -COR⁸, -C(O)OR⁸, -OC(O)R⁸, -OC(O)OR⁸, -SR⁸, -S(O)R⁸, or -S(O)₂R⁸;

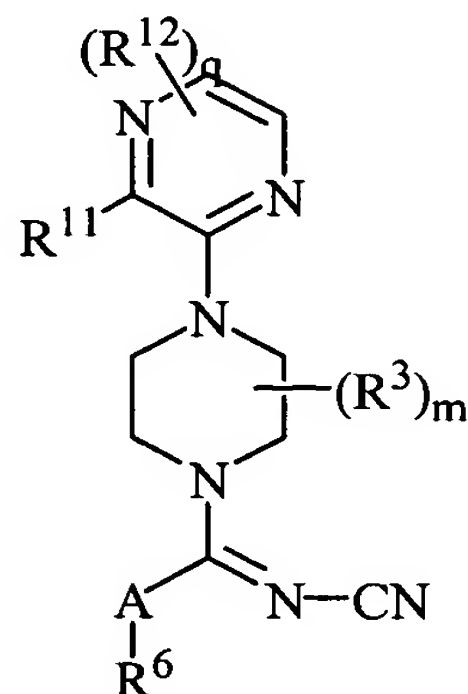
each R⁸ is independently -H, -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₃-C₈)cycloalkyl, -(C₅-C₈)cycloalkenyl, -phenyl, -(C₃-C₅)heterocycle, -C(halo)₃, -CH₂(halo), or -CH(halo)₂;

each halo is independently -F, -Cl, -Br or -I;

n is an integer ranging from 0 to 2; and

m is an integer ranging from 0 to 2.

The present invention also encompasses compounds having the formula (IIa):



(IIa)

and pharmaceutically acceptable salts thereof, wherein:

A is -NR⁴-, -O-, or -S-;

each R³ is independently:

(a) -halo, -CN, -OH, -NO₂, or -NH₂;

5 (b) -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(C₃-C₇)heterocycle, or -(C₇-C₁₀)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R⁵ groups; or

10 (c) -phenyl, -naphthyl, -(C₁₄)aryl or -(C₅-C₁₀)heteroaryl, each of which is unsubstituted or substituted with one or more R⁷ groups;

R⁴ is hydrogen, -(C₁-C₆)alkyl, or -O-(C₁-C₆)alkyl;

each R⁵ is independently -CN, -OH, -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -

(C₂-C₆)alkenyl, -halo, -N₃, -NO₂, -N(R⁸)₂, -CH=NR⁸, -NR⁸OH, -OR⁸, -COR⁸, -C(O)OR⁸,

15 -OC(O)R⁸, -OC(O)OR⁸, -SR⁸, -S(O)R⁸, or -S(O)₂R⁸;

R⁶ is -phenyl, -naphthyl, -(C₃-C₈)cycloalkyl, -(C₁₄)aryl, or -(C₅-C₁₀)heteroaryl,

each of which is unsubstituted or substituted with one or more R⁷ groups;

each R⁷ is independently -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl,

-(C₃-C₈)cycloalkyl, -(C₅-C₈)cycloalkenyl, -phenyl, -(C₃-C₅)heterocycle, -C(halo)₃,

20 -CH₂(halo), -CH(halo)₂, -CN, -OH, -halo, -N₃, -NO₂, -N(R⁸)₂, -CH=NR⁸, -NR⁸OH, -OR⁸,

-COR⁸, -C(O)OR⁸, -OC(O)R⁸, -OC(O)OR⁸, -SR⁸, -S(O)R⁸, or -S(O)₂R⁸;

each R⁸ is independently -H, -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl,

-(C₃-C₈)cycloalkyl, -(C₅-C₈)cycloalkenyl, -phenyl, -(C₃-C₅)heterocycle, -C(halo)₃,

-CH₂(halo), or -CH(halo)₂;

25 R¹¹ is -hydrogen, -halo, -CH₃, -NO₂, -CN, -OH, -OCH₃, -NH₂, -C(halo)₃, -

CH(halo)₂, or -CH₂(halo);

each R¹² is independently:

(a) -halo, -CN, -OH, -NO₂, or -NH₂;

30 (b) -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(C₃-

C₇)heterocycle, or -(C₇-C₁₀)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R⁵ groups; or

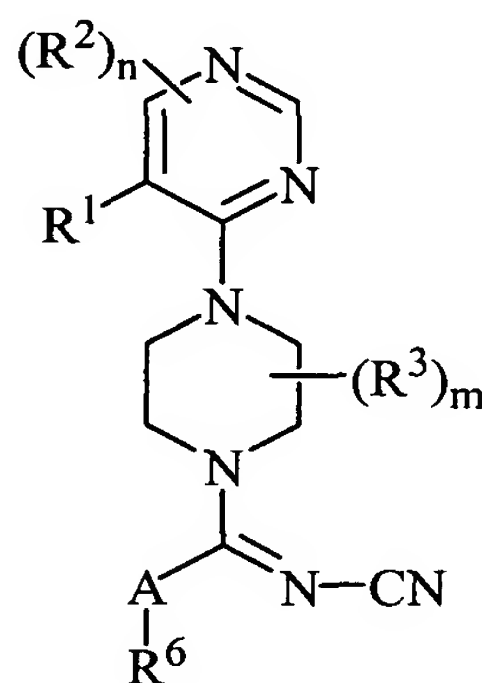
(c) -phenyl, -naphthyl, -(C₁₄)aryl, or -(C₅-C₁₀)heteroaryl, each of which is unsubstituted or substituted with one or more R⁷ groups; and

each halo is independently -F, -Cl, -Br or -I;

q is an integer ranging from 0 to 2; and

m is an integer ranging from 0 to 2.

The present invention also encompasses compounds having the formula (III):



(III)

and pharmaceutically acceptable salts thereof, wherein:

A is -NR⁴-, -O-, or -S-;

R¹ is -halo, -CH₃, -NO₂, -CN, -OH, -OCH₃, -NH₂, -C(halo)₃, -CH(halo)₂, or -CH₂(halo);

each R² is independently:

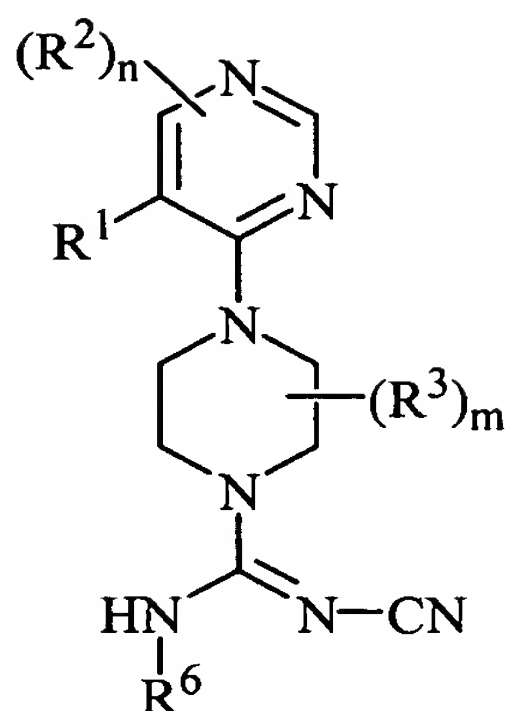
(a) -halo, -CN, -OH, -NO₂, or -NH₂;

(b) -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(C₃-C₇)heterocycle, or -(C₇-C₁₀)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R⁵ groups; or

(c) -phenyl, -naphthyl, -(C₁₄)aryl, or -(C₅-C₁₀)heteroaryl, each of which is unsubstituted or substituted with one or more R⁷ groups;

each R³ is independently:

- (a) -halo, -CN, -OH, -NO₂, or -NH₂;
- (b) -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(C₃-C₇)heterocycle, or -(C₇-C₁₀)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R⁵ groups; or
- (c) -phenyl, -naphthyl, -(C₁₄)aryl or -(C₅-C₁₀)heteroaryl, each of which is unsubstituted or substituted with one or more R⁷ groups;
- R⁴ is -(C₁-C₆)alkyl, or -O-(C₁-C₆)alkyl;
- each R⁵ is independently -CN, -OH, -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -halo, -N₃, -NO₂, -N(R⁸)₂, -CH=NR⁸, -NR⁸OH, -OR⁸, -COR⁸, -C(O)OR⁸, -OC(O)R⁸, -OC(O)OR⁸, -SR⁸, -S(O)R⁸, or -S(O)₂R⁸;
- R⁶ is -phenyl, -naphthyl, -(C₃-C₈)cycloalkyl, -(C₁₄)aryl, or -(C₅-C₁₀)heteroaryl, each of which is unsubstituted or substituted with one or more R⁷ groups;
- each R⁷ is independently -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₃-C₈)cycloalkyl, -(C₅-C₈)cycloalkenyl, -phenyl, -(C₃-C₅)heterocycle, -C(halo)₃, -CH(halo)₂, -CH₂(halo), -CN, -OH, -halo, -N₃, -NO₂, -N(R⁸)₂, -CH=NR⁸, -NR⁸OH, -OR⁸, -COR⁸, -C(O)OR⁸, -OC(O)R⁸, -OC(O)OR⁸, -SR⁸, -S(O)R⁸, or -S(O)₂R⁸;
- each R⁸ is independently -H, -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₃-C₈)cycloalkyl, -(C₅-C₈)cycloalkenyl, -phenyl, -(C₃-C₅)heterocycle, -C(halo)₃, -CH₂(halo), or -CH(halo)₂;
- each halo is independently -F, -Cl, -Br or -I;
- n is an integer ranging from 0 to 2; and
- m is an integer ranging from 0 to 2.
- The present invention encompasses compounds having the formula (IIIa):



(IIIa)

10 and pharmaceutically acceptable salts thereof, wherein:

R^1 is -halo, -CH₃, -NO₂, -CN, -OH, -OCH₃, -NH₂, -C(halo)₃, -CH(halo)₂, or -CH₂(halo);

each R^2 is independently:

- (a) -halo, -CN, -OH, -NO₂, or -NH₂;
- 15 (b) -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(C₃-C₇)heterocycle, or -(C₇-C₁₀)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R^5 groups; or
- 20 (c) -phenyl, -naphthyl, -(C₁₄)aryl, or -(C₅-C₁₀)heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups;

each R^3 is independently:

- (a) -halo, -CN, -OH, -NO₂, or -NH₂; or
- 25 (b) -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(C₃-C₇)heterocycle, or -(C₇-C₁₀)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R^5 groups; or
- 30 (c) -phenyl, -naphthyl, -(C₁₄)aryl or -(C₅-C₁₀)heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups;

each R⁵ is independently -CN, -OH, -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -halo, -N₃, -NO₂, -N(R⁸)₂, -CH=NR⁸, -NR⁸OH, -OR⁸, -COR⁸, -C(O)OR⁸, -OC(O)R⁸, -OC(O)OR⁸, -SR⁸, -S(O)R⁸, or -S(O)₂R⁸;

R⁶ is:

5 (a), -naphthyl, -(C₁₄)aryl, or -(C₃-C₈)cycloalkyl each of which is unsubstituted or substituted with one or more R⁷ groups; or

(b) pyridyl, furyl, benzofuranyl, thiophenyl, benzothiophenyl, quinolinyl, indolyl, oxazolyl, benzoxazolyl, imidazolyl, benzimidazolyl, thiazolyl, benzothiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiadiazolyl, triazinyl, cinnolinyl, phthalazinyl, or quinazolinyl, each of which is substituted with one or more R⁷ groups;

10 each R⁷ is independently -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₃-C₈)cycloalkyl, -(C₅-C₈)cycloalkenyl, -phenyl, -(C₃-C₅)heterocycle, -C(halo)₃, -CH(halo)₂, -CH₂(halo), -CN, -OH, -halo, -N₃, -NO₂, -N(R⁸)₂, -CH=NR⁸, -NR⁸OH, -OR⁸, -COR⁸, -C(O)OR⁸, -OC(O)R⁸, -OC(O)OR⁸, -SR⁸, -S(O)R⁸, or -S(O)₂R⁸;

15 each R⁸ is independently -H, -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₃-C₈)cycloalkyl, -(C₅-C₈)cycloalkenyl, -phenyl, -(C₃-C₅)heterocycle, -C(halo)₃, -CH₂(halo), or -CH(halo)₂;

each halo is independently -F, -Cl, -Br or -I;

20 n is an integer ranging from 0 to 2; and

m is an integer ranging from 0 to 2.

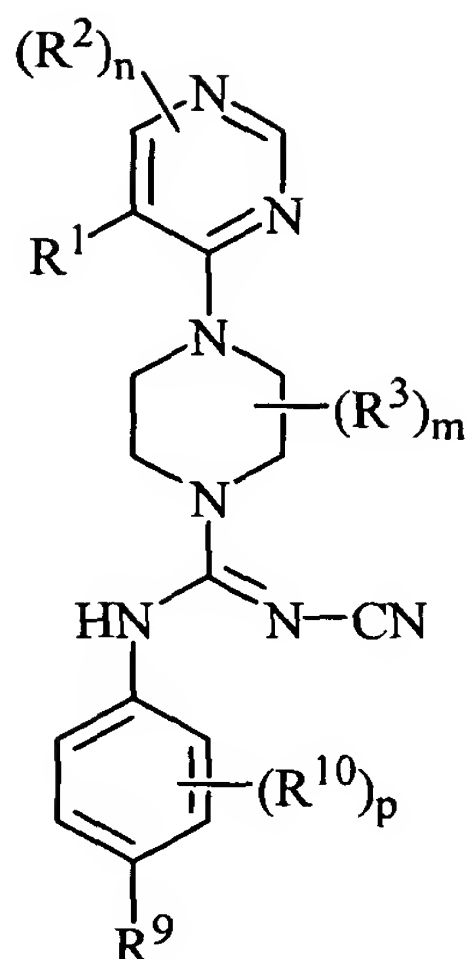
The present invention encompasses compounds having the formula (IIIb):

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(IIIb)

and pharmaceutically acceptable salts thereof, wherein:

R^1 is -halo, -CH₃, -NO₂, -CN, -OH, -OCH₃, -NH₂, -C(halo)₃, -CH(halo)₂, or
15 -CH₂(halo);

each R^2 is independently:

- (a) -halo, -CN, -OH, -NO₂, or -NH₂;
- (b) -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-
C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-
20 C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(C₃-
C₇)heterocycle, or -(C₇-C₁₀)bicycloheterocycle, each of which is unsubstituted
or substituted with one or more R^5 groups; or

- (c) -phenyl, -naphthyl, -(C₁₄)aryl, or -(C₅-C₁₀)heteroaryl, each of
which is unsubstituted or substituted with one or more R^7 groups;

25 each R^3 is independently:

- (a) -halo, -CN, -OH, -NO₂, or -NH₂; or
- (b) -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-
C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-
C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(C₃-
30 C₇)heterocycle, or -(C₇-C₁₀)bicycloheterocycle, each of which is unsubstituted
or substituted with one or more R^5 groups; or

(c) -phenyl, -naphthyl, -(C₁₄)aryl or -(C₅-C₁₀)heteroaryl, each of which is unsubstituted or substituted with one or more R⁷ groups;

each R⁵ is independently -CN, -OH, -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -halo, -N₃, -NO₂, -N(R⁸)₂, -CH=NR⁸, -NR⁸OH, -OR⁸, -COR⁸, -C(O)OR⁸,
5 -OC(O)R⁸, -OC(O)OR⁸, -SR⁸, -S(O)R⁸, or -S(O)₂R⁸;

each R⁷, R⁹, and R¹⁰ is independently -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₃-C₈)cycloalkyl, -(C₅-C₈)cycloalkenyl, -phenyl, -(C₃-C₅)heterocycle, -C(halo)₃, -CH(halo)₂, -CH₂(halo), -CN, -OH, -halo, -N₃, -NO₂, -N(R⁸)₂, -CH=NR⁸, -NR⁸OH, -OR⁸, -COR⁸, -C(O)OR⁸, -OC(O)R⁸, -OC(O)OR⁸, -SR⁸, -S(O)R⁸, or -S(O)₂R⁸;

10 each R⁸ is independently -H, -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₃-C₈)cycloalkyl, -(C₅-C₈)cycloalkenyl, -phenyl, -(C₃-C₅)heterocycle, -C(halo)₃, -CH₂(halo), or -CH(halo)₂;

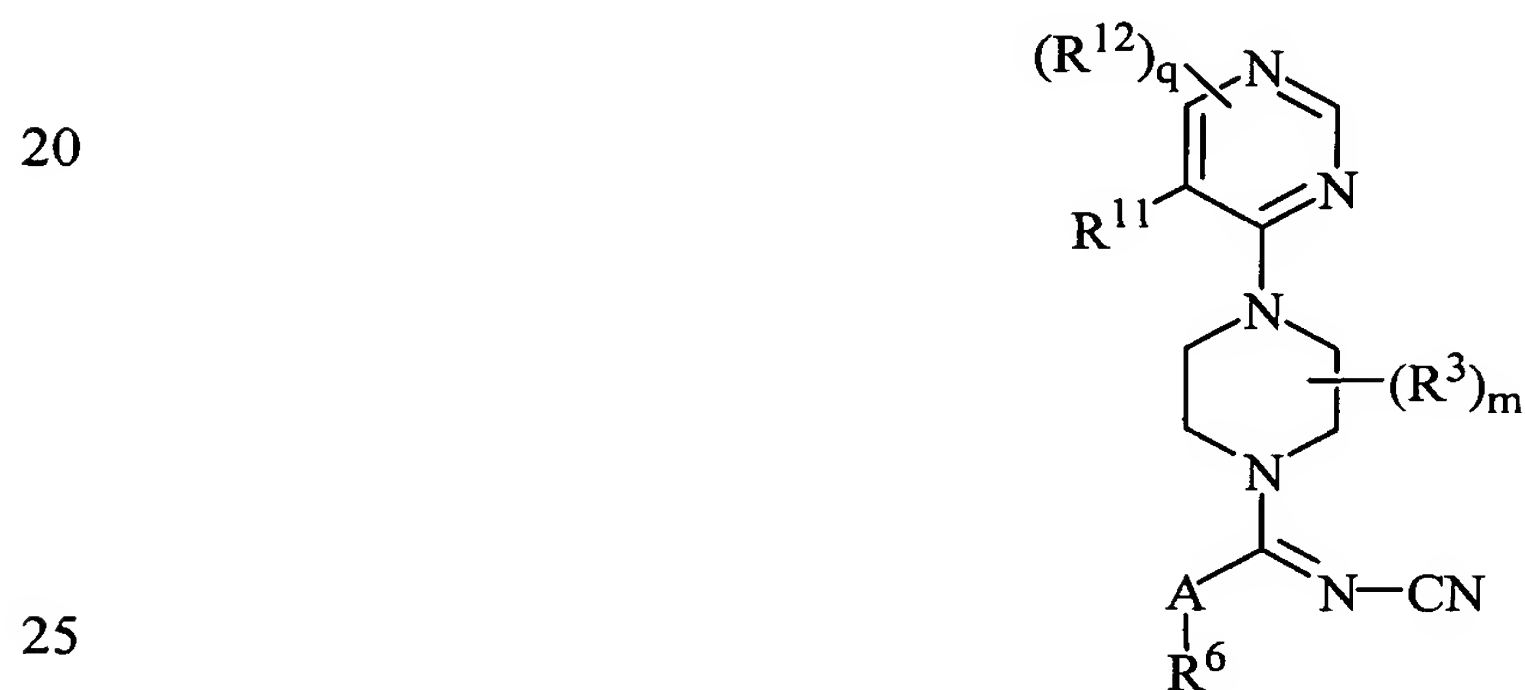
each halo is independently -F, -Cl, -Br or -I;

n is an integer ranging from 0 to 2;

15 m is an integer ranging from 0 to 2; and

p is an integer ranging from 0 to 4.

The present invention also encompasses compounds having the formula (IIIc):



(IIIc)

and pharmaceutically acceptable salts thereof, wherein:

A is -NR⁴-, -O-, or -S-;

30 each R³ is independently:

(a) -halo, -CN, -OH, -NO₂, or -NH₂;

- (b) $-(C_1-C_{10})$ alkyl, $-(C_2-C_{10})$ alkenyl, $-(C_2-C_{10})$ alkynyl, $-(C_3-C_{10})$ cycloalkyl, $-(C_8-C_{14})$ bicycloalkyl, $-(C_8-C_{14})$ tricycloalkyl, $-(C_5-C_{10})$ cycloalkenyl, $-(C_8-C_{14})$ bicycloalkenyl, $-(C_8-C_{14})$ tricycloalkenyl, $-(C_3-C_7)$ heterocycle, or $-(C_7-C_{10})$ bicycloheterocycle, each of which is unsubstituted or substituted with one or more R^5 groups; or
- (c) -phenyl, -naphthyl, $-(C_{14})$ aryl or $-(C_5-C_{10})$ heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups;
- R^4 is $-(C_1-C_6)$ alkyl, or $-O-(C_1-C_6)$ alkyl;
- each R^5 is independently -CN, -OH, $-(C_1-C_6)$ alkyl, $-(C_2-C_6)$ alkenyl, $-(C_2-C_6)$ alkynyl, $-(C_2-C_6)$ alkenyl, -halo, $-N_3$, $-NO_2$, $-N(R^8)_2$, $-CH=NR^8$, $-NR^8OH$, $-OR^8$, $-COR^8$, $-C(O)OR^8$, $-OC(O)R^8$, $-OC(O)OR^8$, $-SR^8$, $-S(O)R^8$, or $-S(O)_2R^8$;
- R^6 is -phenyl, -naphthyl, $-(C_3-C_8)$ cycloalkyl, $-(C_{14})$ aryl, or $-(C_5-C_{10})$ heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups;
- each R^7 is independently $-(C_1-C_6)$ alkyl, $-(C_2-C_6)$ alkenyl, $-(C_2-C_6)$ alkynyl, $-(C_3-C_8)$ cycloalkyl, $-(C_5-C_8)$ cycloalkenyl, -phenyl, $-(C_3-C_5)$ heterocycle, $-C(halo)_3$, $-CH(halo)_2$, $-CH_2(halo)$, -CN, -OH, -halo, $-N_3$, $-NO_2$, $-N(R^8)_2$, $-CH=NR^8$, $-NR^8OH$, $-OR^8$, $-COR^8$, $-C(O)OR^8$, $-OC(O)R^8$, $-OC(O)OR^8$, $-SR^8$, $-S(O)R^8$, or $-S(O)_2R^8$;
- each R^8 is independently -H, $-(C_1-C_6)$ alkyl, $-(C_2-C_6)$ alkenyl, $-(C_2-C_6)$ alkynyl, $-(C_3-C_8)$ cycloalkyl, $-(C_5-C_8)$ cycloalkenyl, -phenyl, $-(C_3-C_5)$ heterocycle, $-C(halo)_3$, $-CH_2(halo)$, or $-CH(halo)_2$;
- R^{11} is -hydrogen, -halo, $-CH_3$, $-NO_2$, -CN, -OH, $-OCH_3$, $-NH_2$, $-C(halo)_3$, $-CH(halo)_2$, or $-CH_2(halo)$;
- each R^{12} is independently:
- (a) -halo, -CN, -OH, $-NO_2$, or $-NH_2$;
- (b) $-(C_1-C_{10})$ alkyl, $-(C_2-C_{10})$ alkenyl, $-(C_2-C_{10})$ alkynyl, $-(C_3-C_{10})$ cycloalkyl, $-(C_8-C_{14})$ bicycloalkyl, $-(C_8-C_{14})$ tricycloalkyl, $-(C_5-C_{10})$ cycloalkenyl, $-(C_8-C_{14})$ bicycloalkenyl, $-(C_8-C_{14})$ tricycloalkenyl, $-(C_3-C_7)$ heterocycle, or $-(C_7-C_{10})$ bicycloheterocycle, each of which is unsubstituted or substituted with one or more R^5 groups; or
- (c) -phenyl, -naphthyl, $-(C_{14})$ aryl, or $-(C_5-C_{10})$ heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups;

each halo is independently -F, -Cl, -Br or -I;

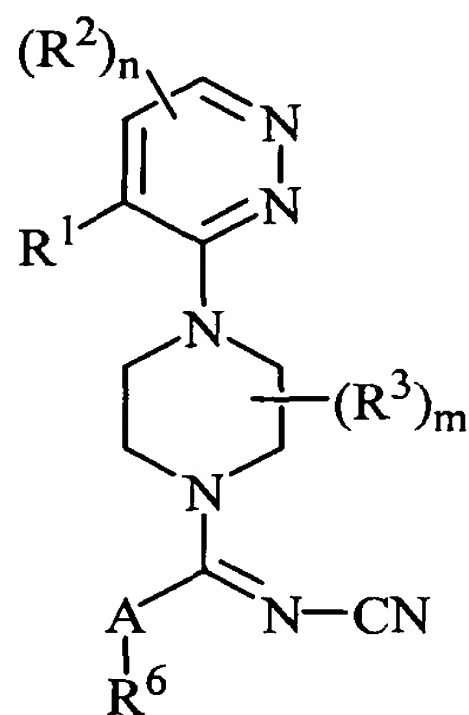
q is an integer ranging from 0 to 2; and

m is an integer ranging from 0 to 2.

The present invention also encompasses compounds having the formula (IV):

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(IV)

15 and pharmaceutically acceptable salts thereof, wherein:

A is $-NR^4-$, $-O-$, or $-S-$;

R^1 is -halo, $-CH_3$, $-NO_2$, $-CN$, $-OH$, $-OCH_3$, $-NH_2$, $-C(halo)_3$, $-CH(halo)_2$, or $-CH_2(halo)$;

each R^2 is independently:

20

(a) -halo, $-CN$, $-OH$, $-NO_2$, or $-NH_2$;

(b) $-(C_1-C_{10})$ alkyl, $-(C_2-C_{10})$ alkenyl, $-(C_2-C_{10})$ alkynyl, $-(C_3-C_{10})$ cycloalkyl, $-(C_8-C_{14})$ bicycloalkyl, $-(C_8-C_{14})$ tricycloalkyl, $-(C_5-C_{10})$ cycloalkenyl, $-(C_8-C_{14})$ bicycloalkenyl, $-(C_8-C_{14})$ tricycloalkenyl, $-(C_3-C_7)$ heterocycle, or $-(C_7-C_{10})$ bicycloheterocycle, each of which is unsubstituted or substituted with one or more R^5 groups; or

25

(c) -phenyl, -naphthyl, $-(C_{14})$ aryl, or $-(C_5-C_{10})$ heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups;

each R^3 is independently:

30

(a) -halo, $-CN$, $-OH$, $-NO_2$, or $-NH_2$;

(b) $-(C_1-C_{10})$ alkyl, $-(C_2-C_{10})$ alkenyl, $-(C_2-C_{10})$ alkynyl, $-(C_3-C_{10})$ cycloalkyl, $-(C_8-C_{14})$ bicycloalkyl, $-(C_8-C_{14})$ tricycloalkyl, $-(C_5-$

C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(C₃-C₇)heterocycle, or -(C₇-C₁₀)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R⁵ groups; or

(c) -phenyl, -naphthyl, -(C₁₄)aryl or -(C₅-C₁₀)heteroaryl, each of which is unsubstituted or substituted with one or more R⁷ groups;

R⁴ is hydrogen, -(C₁-C₆)alkyl, or -O-(C₁-C₆)alkyl;

each R⁵ is independently -CN, -OH, -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkenyl, -halo, -N₃, -NO₂, -N(R⁸)₂, -CH=NR⁸, -NR⁸OH, -OR⁸, -COR⁸, -C(O)OR⁸, -OC(O)R⁸, -OC(O)OR⁸, -SR⁸, -S(O)R⁸, or -S(O)₂R⁸;

R⁶ is -phenyl, -naphthyl, -(C₃-C₈)cycloalkyl, -(C₁₄)aryl, or -(C₅-C₁₀)heteroaryl, each of which is unsubstituted or substituted with one or more R⁷ groups;

each R⁷ is independently -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₃-C₈)cycloalkyl, -(C₅-C₈)cycloalkenyl, -phenyl, -(C₃-C₅)heterocycle, -C(halo)₃, -CH(halo)₂, -CH₂(halo), -CN, -OH, -halo, -N₃, -NO₂, -N(R⁸)₂, -CH=NR⁸, -NR⁸OH, -OR⁸, -COR⁸, -C(O)OR⁸, -OC(O)R⁸, -OC(O)OR⁸, -SR⁸, -S(O)R⁸, or -S(O)₂R⁸;

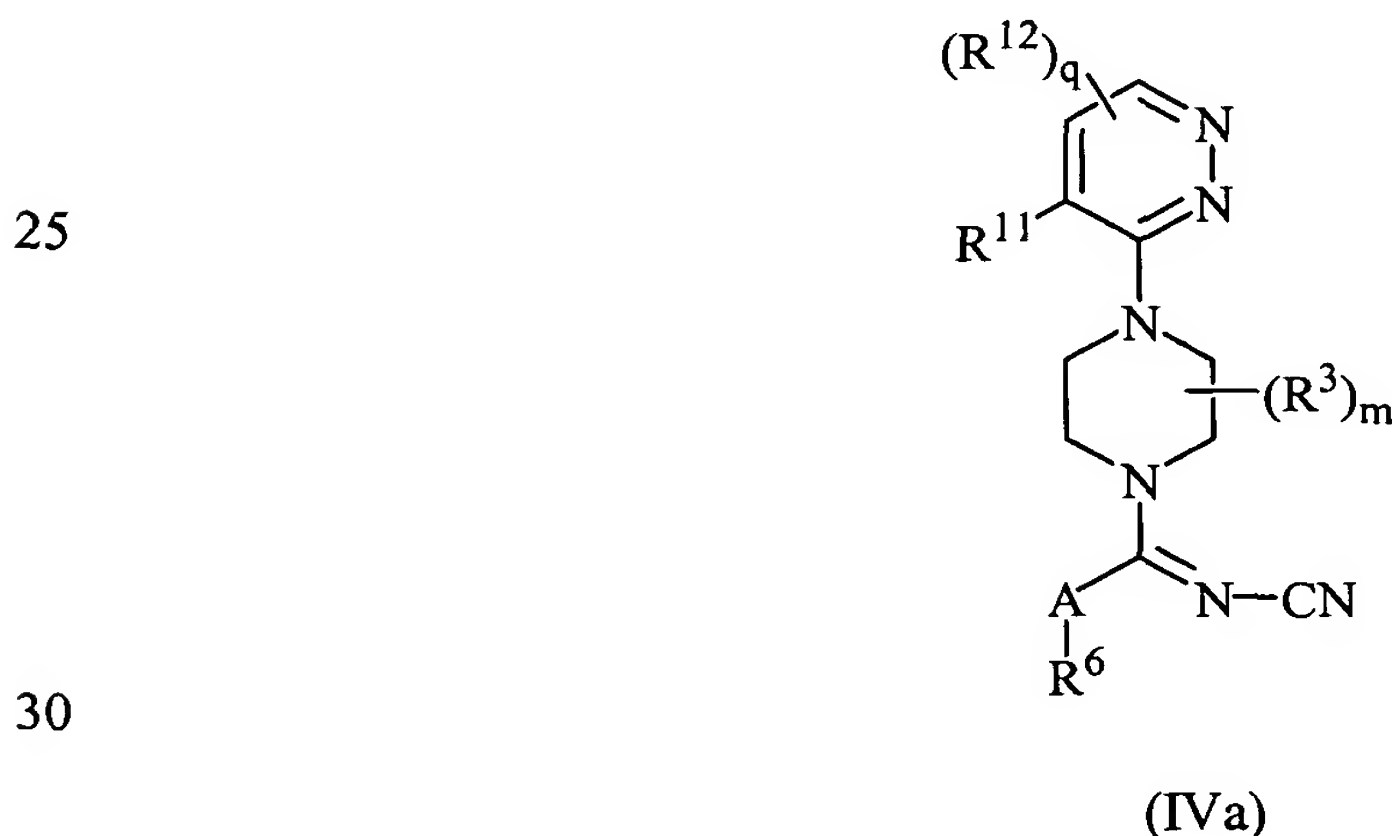
each R⁸ is independently -H, -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₃-C₈)cycloalkyl, -(C₅-C₈)cycloalkenyl, -phenyl, -(C₃-C₅)heterocycle, -C(halo)₃, -CH₂(halo), or -CH(halo)₂;

each halo is independently -F, -Cl, -Br or -I;

n is an integer ranging from 0 to 2; and

m is an integer ranging from 0 to 2.

The present invention also encompasses compounds having the formula (IVa):



and pharmaceutically acceptable salts thereof, wherein:

A is -NR⁴-, -O-, or -S-;

each R³ is independently:

(a) -halo, -CN, -OH, -NO₂, or -NH₂;

5 (b) -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(C₃-C₇)heterocycle, or -(C₇-C₁₀)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R⁵ groups; or

10 (c) -phenyl, -naphthyl, -(C₁₄)aryl or -(C₅-C₁₀)heteroaryl, each of which is unsubstituted or substituted with one or more R⁷ groups;

R⁴ is hydrogen, -(C₁-C₆)alkyl, or -O-(C₁-C₆)alkyl;

each R⁵ is independently -CN, -OH, -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkenyl, -halo, -N₃, -NO₂, -N(R⁸)₂, -CH=NR⁸, -NR⁸OH, -OR⁸, -COR⁸, -C(O)OR⁸,
15 -OC(O)R⁸, -OC(O)OR⁸, -SR⁸, -S(O)R⁸, or -S(O)₂R⁸;

R⁶ is -phenyl, -naphthyl, -(C₃-C₈)cycloalkyl, -(C₁₄)aryl, or -(C₅-C₁₀)heteroaryl, each of which is unsubstituted or substituted with one or more R⁷ groups;

each R⁷ is independently -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₃-C₈)cycloalkyl, -(C₅-C₈)cycloalkenyl, -phenyl, -(C₃-C₅)heterocycle, -C(halo)₃,
20 -CH(halo)₂, -CH₂(halo), -CN, -OH, -halo, -N₃, -NO₂, -N(R⁸)₂, -CH=NR⁸, -NR⁸OH, -OR⁸, -COR⁸, -C(O)OR⁸, -OC(O)R⁸, -OC(O)OR⁸, -SR⁸, -S(O)R⁸, or -S(O)₂R⁸;

each R⁸ is independently -H, -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₃-C₈)cycloalkyl, -(C₅-C₈)cycloalkenyl, -phenyl, -(C₃-C₅)heterocycle, -C(halo)₃, -CH₂(halo), or -CH(halo)₂;

25 R¹¹ is -hydrogen, -halo, -CH₃, -NO₂, -CN, -OH, -OCH₃, -NH₂, -C(halo)₃, -CH(halo)₂, or -CH₂(halo);

each R¹² is independently:

(a) -halo, -CN, -OH, -NO₂, or -NH₂;

30 (b) -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(C₃-

C₇)heterocycle, or -(C₇-C₁₀)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R⁵ groups; or

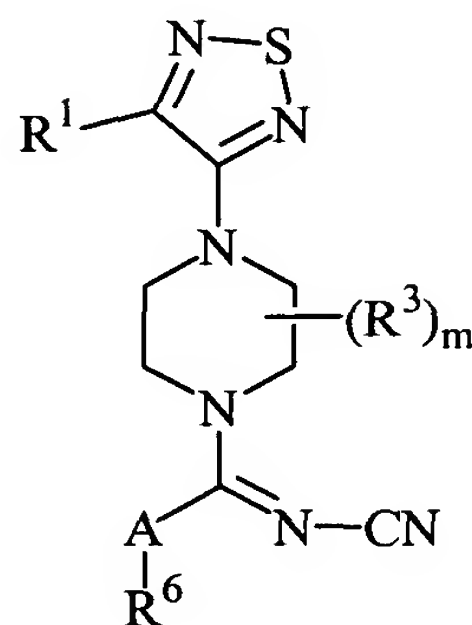
(c) -phenyl, -naphthyl, -(C₁₄)aryl, or -(C₅-C₁₀)heteroaryl, each of which is unsubstituted or substituted with one or more R⁷ groups;

each halo is independently -F, -Cl, -Br or -I;

q is an integer ranging from 0 to 2; and

m is an integer ranging from 0 to 2.

The present invention also encompasses compounds having the formula (V):



(V)

and pharmaceutically acceptable salts thereof, wherein:

A is -NR⁴-, -O-, or -S-;

R¹ is -hydrogen, -halo, -CH₃, -NO₂, -CN, -OH, -OCH₃, -NH₂, -C(halo)₃, -

CH(halo)₂, or -CH₂(halo);

each R³ is independently:

(a) -halo, -CN, -OH, -NO₂, or -NH₂;

(b) -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(C₃-C₇)heterocycle, or -(C₇-C₁₀)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R⁵ groups; or

(c) -phenyl, -naphthyl, -(C₁₄)aryl or -(C₅-C₁₀)heteroaryl, each of which is unsubstituted or substituted with one or more R⁷ groups;

R⁴ is hydrogen, -(C₁-C₆)alkyl, or -O-(C₁-C₆)alkyl;

each R^5 is independently -CN, -OH, $-(C_1-C_6)alkyl$, $-(C_2-C_6)alkenyl$, $-(C_2-C_6)alkenyl$, -halo, $-N_3$, $-NO_2$, $-N(R^8)_2$, $-CH=NR^8$, $-NR^8OH$, $-OR^8$, $-COR^8$, $-C(O)OR^8$, $-OC(O)R^8$, $-OC(O)OR^8$, $-SR^8$, $-S(O)R^8$, or $-S(O)_2R^8$;

R^6 is -phenyl, -naphthyl, $-(C_3-C_8)cycloalkyl$, $-(C_{14})aryl$, or $-(C_5-C_{10})heteroaryl$,

5 each of which is unsubstituted or substituted with one or more R^7 groups;

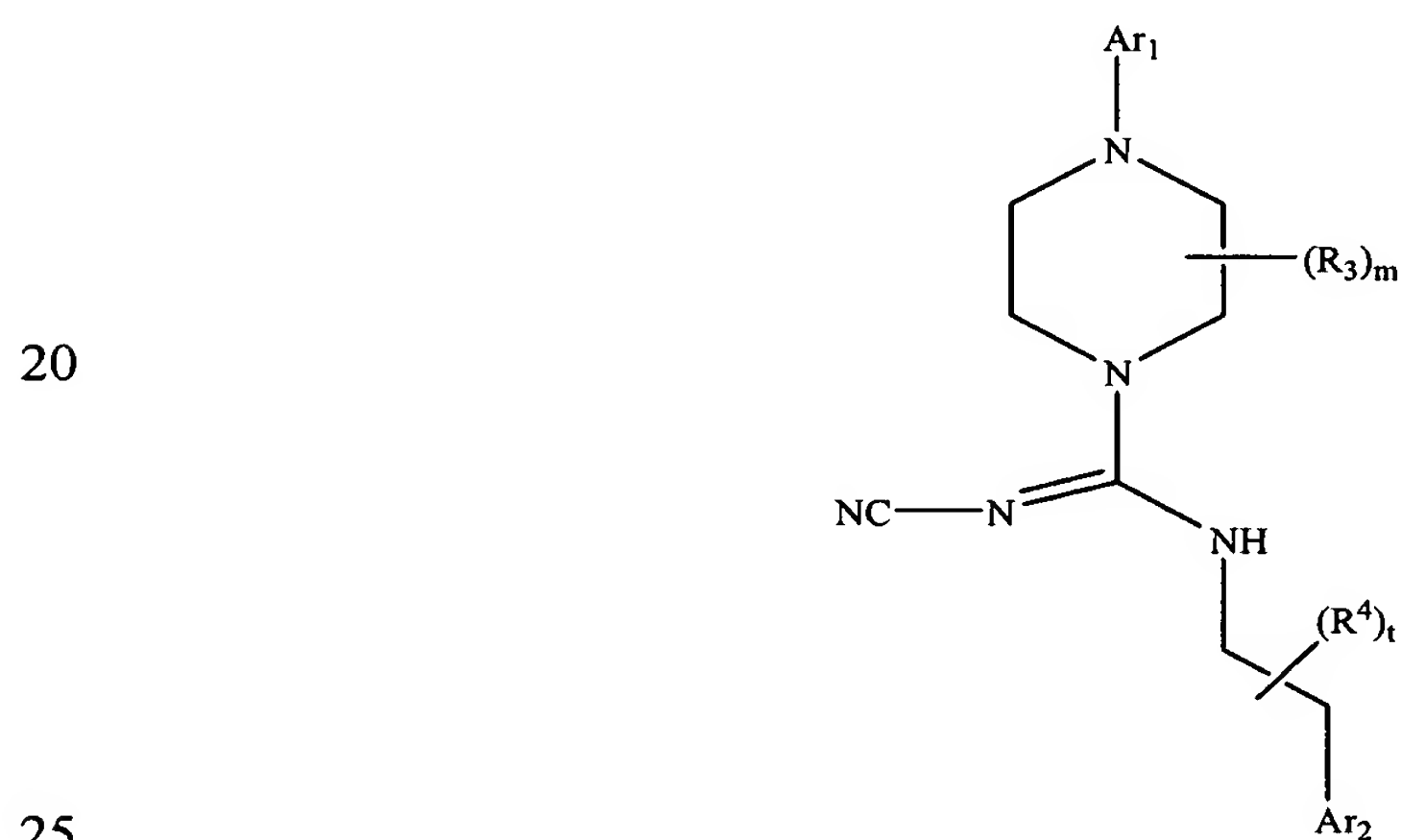
each R^7 is independently $-(C_1-C_6)alkyl$, $-(C_2-C_6)alkenyl$, $-(C_2-C_6)alkynyl$, $-(C_3-C_8)cycloalkyl$, $-(C_5-C_8)cycloalkenyl$, -phenyl, $-(C_3-C_5)heterocycle$, $-C(halo)_3$, $-CH_2(halo)$, $-CH(halo)_2$, -CN, -OH, -halo, $-N_3$, $-NO_2$, $-N(R^8)_2$, $-CH=NR^8$, $-NR^8OH$, $-OR^8$, $-COR^8$, $-C(O)OR^8$, $-OC(O)R^8$, $-OC(O)OR^8$, $-SR^8$, $-S(O)R^8$, or $-S(O)_2R^8$;

10 each R^8 is independently -H, $-(C_1-C_6)alkyl$, $-(C_2-C_6)alkenyl$, $-(C_2-C_6)alkynyl$, $-(C_3-C_8)cycloalkyl$, $-(C_5-C_8)cycloalkenyl$, -phenyl, $-(C_3-C_5)heterocycle$, $-C(halo)_3$, $-CH_2(halo)$, or $-CH(halo)_2$;

each halo is independently -F, -Cl, -Br or -I; and

m is an integer ranging from 0 to 2.

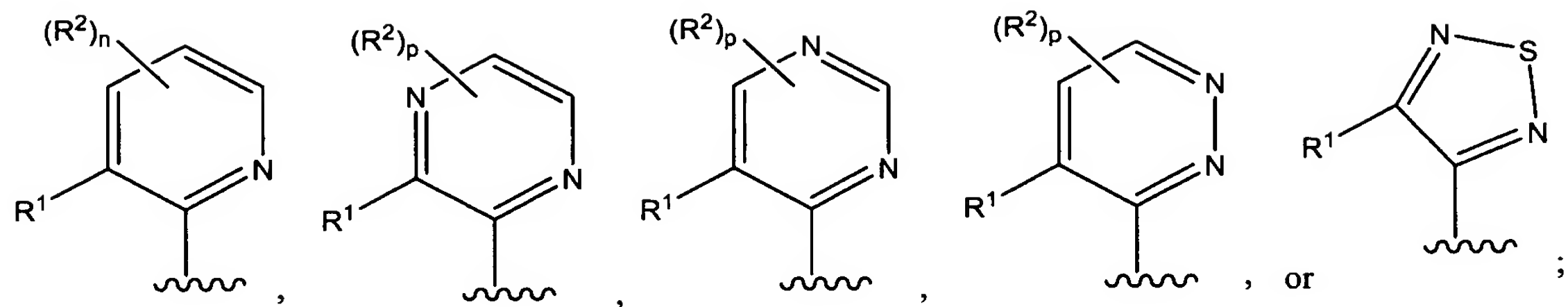
15 The present invention encompasses compounds having the formula (VI):



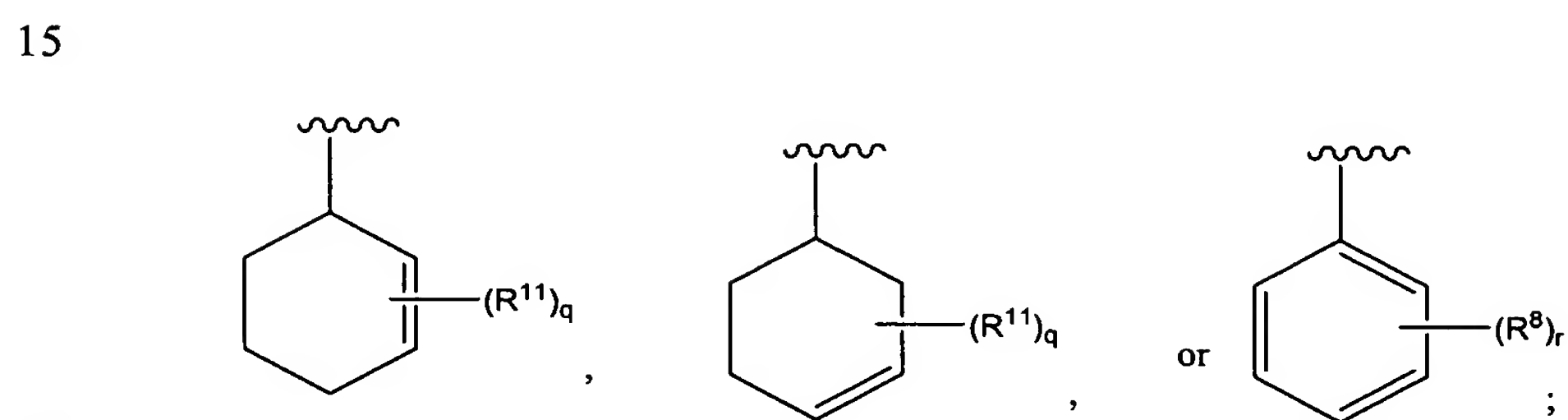
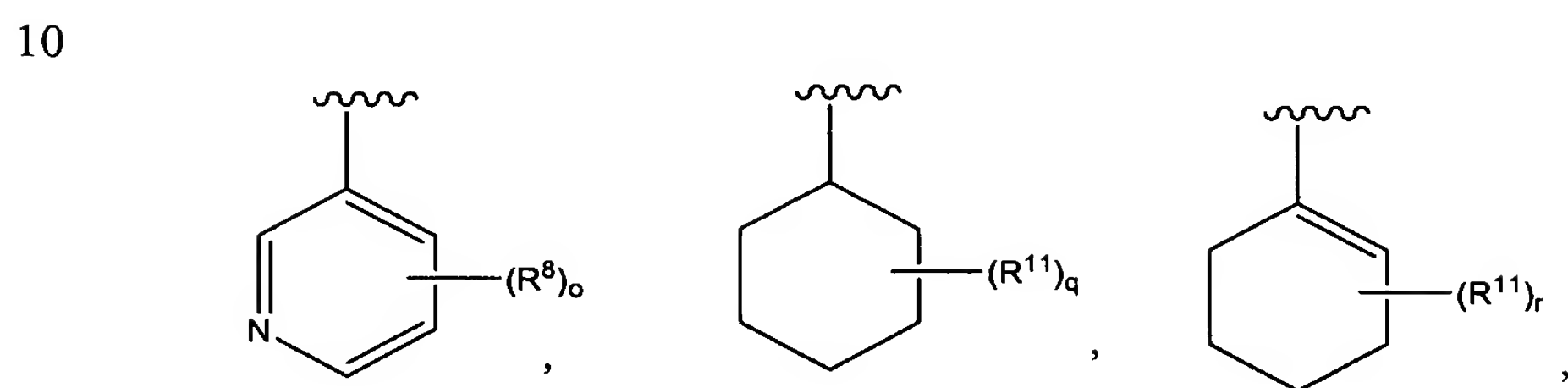
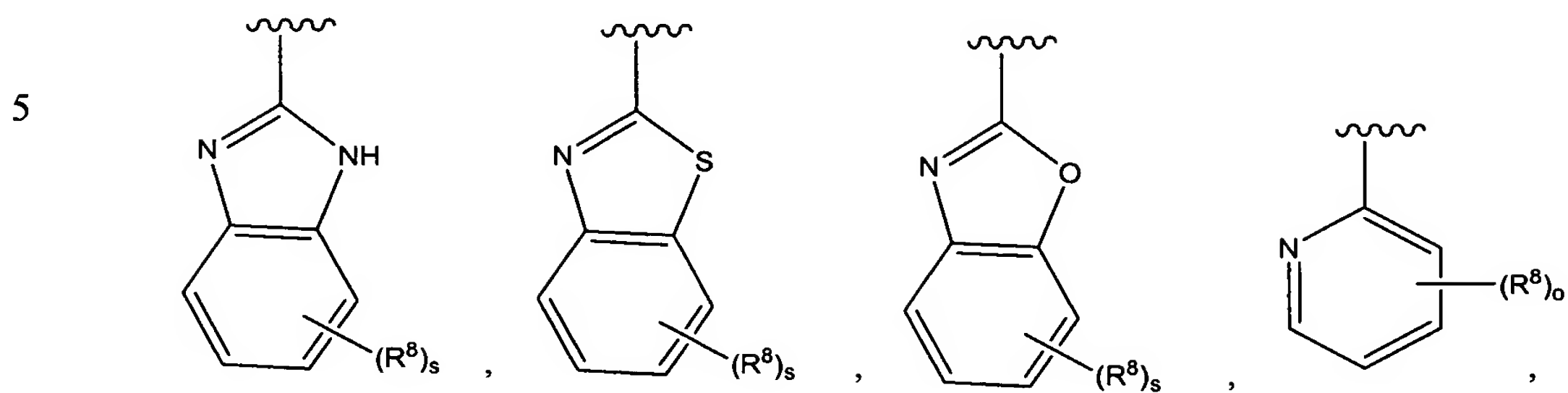
(VI)

and pharmaceutically acceptable salts thereof, wherein:

Ar_1 is



Ar₂ is



R¹ is -H, -halo, -CH₃, -NO₂, -CN, -OH, -OCH₃, -NH₂, C(halo)₃, -CH(halo)₂, or -CH₂(halo);

each R² is independently:

(a) -halo, -CN, -OH, -NO₂, or -NH₂;

5 (b) -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R⁵ groups; or

10 (c) -phenyl, -naphthyl, -(C₁₄)aryl or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R₆ groups;

each R³ is independently:

(a) -halo, -CN, -OH, -NO₂, or -NH₂;

15 (b) -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R⁵ groups; or

20 (c) -phenyl, -naphthyl, -(C₁₄)aryl or -(5- to 10-membered) heteroaryl, each of which is unsubstituted or substituted with one or more R⁶ groups;

each R⁴ is independently -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₃-C₈)cycloalkyl, -(C₅-C₈)cycloalkenyl, -phenyl, -(3- to 5-membered)heterocycle, -C(halo)₃, -CH(halo)₂, or CH₂(halo);

25 each R⁵ is independently -CN, -OH, -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -halo, -N₃, -NO₂, -N(R⁸)₂, -CH=NR⁸, -NR⁸OH, -OR⁸, -COR⁸, -C(O)OR⁸, -OC(O)R⁸, -OC(O)OR⁸, -SR⁸, -S(O)R⁸, or -S(O)₂R⁸;

30 each R⁶ is independently -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₃-C₈)cycloalkyl, -(C₅-C₈)cycloalkenyl, -phenyl, -(3- to 5-membered)heterocycle, -C(halo)₃, -CH(halo)₂, -CH₂(halo), -CN, -OH, -halo, -N₃, -NO₂, -CH=NR₇, -NR₇OH, -OR₇, -COR₇, -C(O)OR₇, -OC(O)R₇, -OC(O)OR₇, -SR₇, -S(O)R₇, or -S(O)₂R₇;

each R^7 is independently -H, $-(C_1-C_6)$ alkyl, $-(C_2-C_6)$ alkenyl, $-(C_2-C_6)$ alkynyl, $-(C_3-C_8)$ cycloalkyl, $-(C_5-C_8)$ cycloalkenyl, -phenyl, -(3- to 5-membered)heterocycle, - $C(halo)_3$, $-CH(halo)_2$, or $CH_2(halo)$;

each R^8 is independently $-(C_1-C_6)$ alkyl, $-(C_2-C_6)$ alkenyl, $-(C_2-C_6)$ alkynyl, $-(C_3-C_8)$ cycloalkyl, $-(C_5-C_8)$ cycloalkenyl, -phenyl, $-C(halo)_3$, $-CH(halo)_2$, $-CH_2(halo)$, -CN, -OH, -halo, $-N_3$, $-NO_2$, $-CH=NR_7$, $-NR_7OH$, $-OR_7$, $-COR_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-OC(O)OR_7$, $-SR_7$, $-S(O)R_7$, or $-S(O)_2R_7$;

each R^{11} is independently -CN, -OH, $-(C_1-C_6)$ alkyl, $-(C_2-C_6)$ alkenyl, -halo, $-N_3$, $-NO_2$, $-N(R_7)_2$, $-CH=NR_7$, $-NR_7OH$, $-OR_7$, $-COR_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-OC(O)OR_7$, $-SR_7$, $-S(O)R_7$, or $-S(O)_2R_7$;

each halo is independently -F, -Cl, -Br, or -I;

m is 0 or 1;

n is an integer ranging from 0 to 3;

o is an integer ranging from 0 to 4;

p is an integer ranging from 0 to 2;

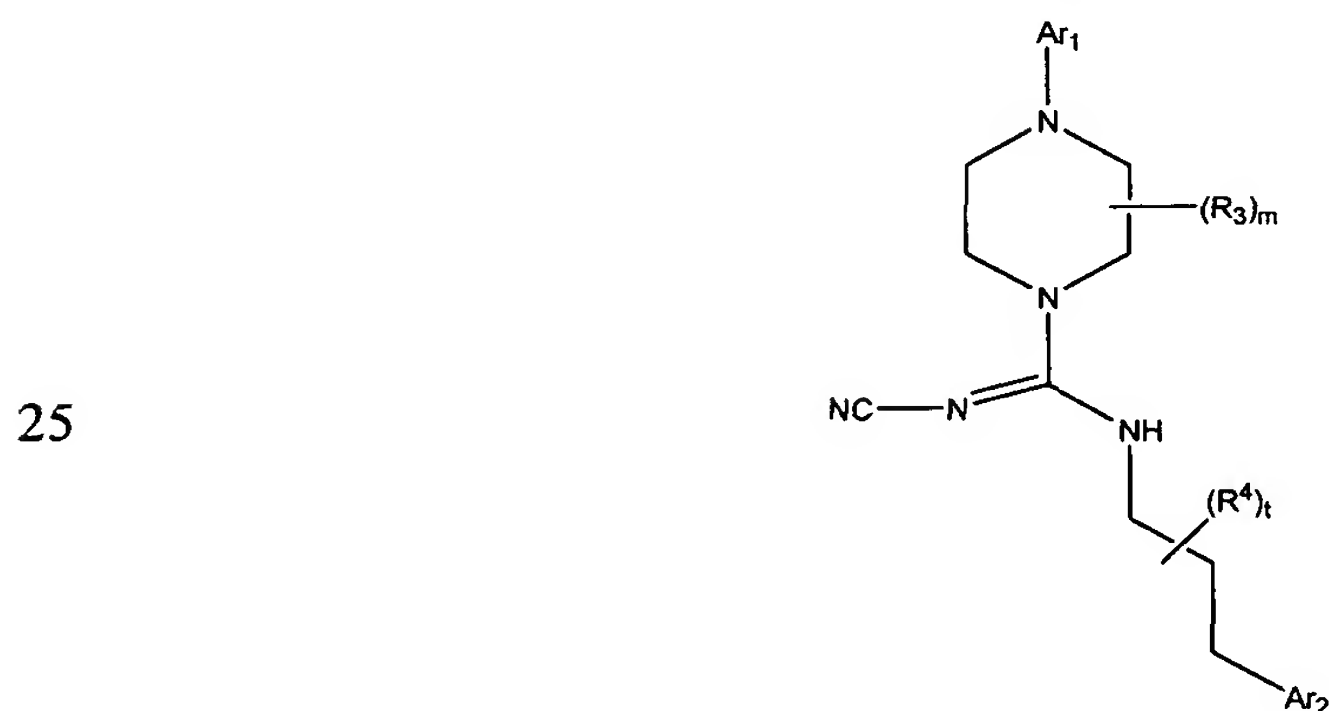
q is an integer ranging from 0 to 6;

r is an integer ranging from 0 to 5;

s is an integer ranging from 0 to 4; and

t is an integer ranging from 0 to 2.

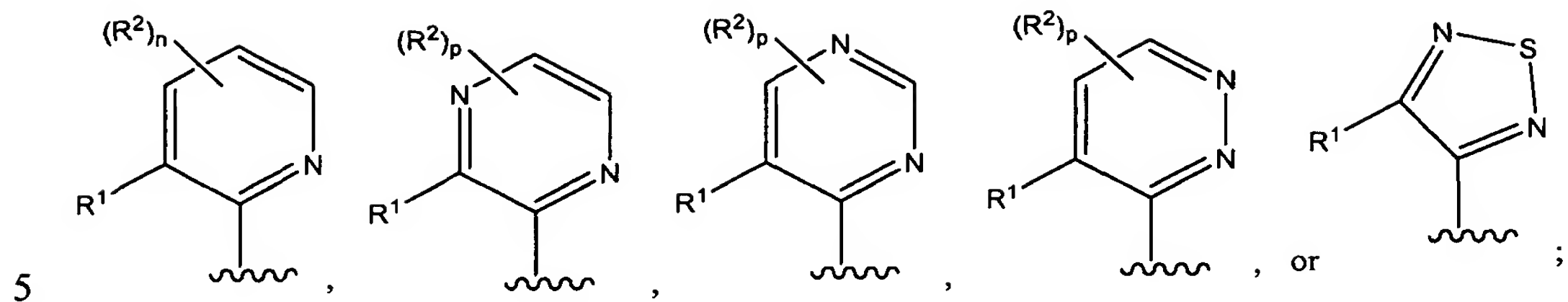
The present invention encompasses compounds having the formula (VII):



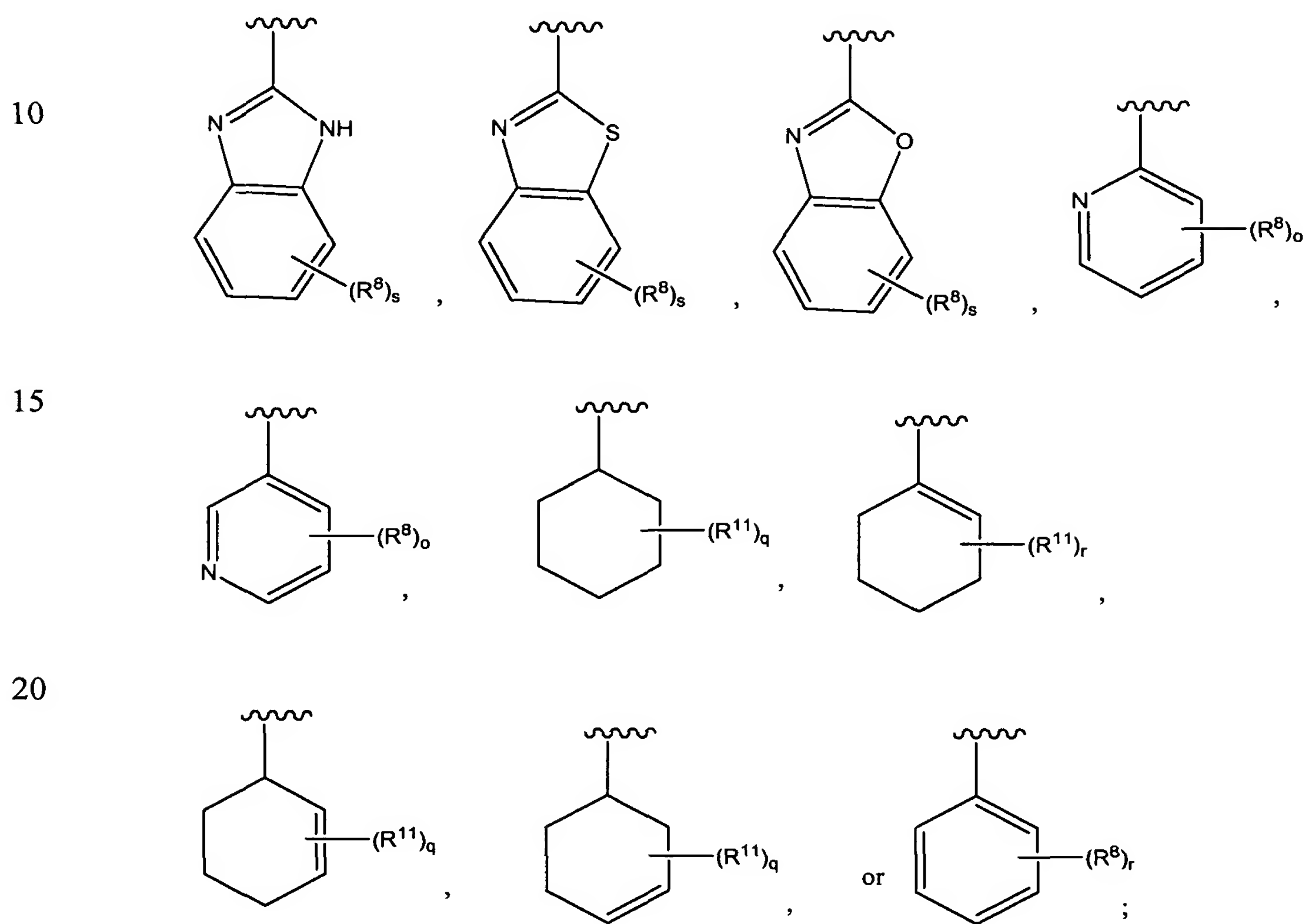
(VII)

and pharmaceutically acceptable salts thereof, wherein:

Ar_1 is



Ar₂ is



25

R¹ is -H, -halo, -CH₃, -NO₂, -CN, -OH, -OCH₃, -NH₂, C(halo)₃, -CH(halo)₂, or -CH₂(halo);

each R² is independently:

(a) -halo, -CN, -OH, -NO₂, or -NH₂;

30 (b) -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-C₁₀)cycloalkenyl, -(C₈-

C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R⁵ groups; or

(c) -phenyl, -naphthyl, -(C₁₄)aryl or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R₆ groups;

each R³ is independently:

(a) -halo, -CN, -OH, -NO₂, or -NH₂;

(b) -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R⁵ groups; or

(c) -phenyl, -naphthyl, -(C₁₄)aryl or -(5- to 10-membered) heteroaryl, each of which is unsubstituted or substituted with one or more R⁶ groups;

each R⁴ is independently -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₃-C₈)cycloalkyl, -(C₅-C₈)cycloalkenyl, -phenyl, -(3- to 5-membered)heterocycle, -C(halo)₃, -CH(halo)₂, or CH₂(halo);

each R⁵ is independently -CN, -OH, -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -halo, -N₃, -NO₂, -N(R⁸)₂, -CH=NR⁸, -NR⁸OH, -OR⁸, -COR⁸, -C(O)OR⁸, -OC(O)R⁸, -OC(O)OR⁸, -SR⁸, -S(O)R⁸, or -S(O)₂R⁸;

each R⁶ is independently -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₃-C₈)cycloalkyl, -(C₅-C₈)cycloalkenyl, -phenyl, -(3- to 5-membered)heterocycle, -C(halo)₃, -CH(halo)₂, -CH₂(halo), -CN, -OH, -halo, -N₃, -NO₂, -CH=NR₇, -NR₇OH, -OR₇, -COR₇, -C(O)OR₇, -OC(O)R₇, -OC(O)OR₇, -SR₇, -S(O)R₇, or -S(O)₂R₇;

each R⁷ is independently -H, -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₃-C₈)cycloalkyl, -(C₅-C₈)cycloalkenyl, -phenyl, -(3- to 5-membered)heterocycle, -C(halo)₃, -CH(halo)₂, or CH₂(halo);

each R⁸ is independently -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₃-C₈)cycloalkyl, -(C₅-C₈)cycloalkenyl, -phenyl, -C(halo)₃, -CH(halo)₂, -CH₂(halo), -CN, -OH, -halo, -N₃, -NO₂, -CH=NR₇, -NR₇OH, -OR₇, -COR₇, -C(O)OR₇, -OC(O)R₇, -OC(O)OR₇, -SR₇, -S(O)R₇, or -S(O)₂R₇;

each R¹¹ is independently -CN, -OH, -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -halo, -N₃, -NO₂, -N(R₇)₂, -CH=NR₇, -NR₇OH, -OR₇, -COR₇, -C(O)OR₇, -OC(O)R₇, -OC(O)OR₇, -SR₇, -S(O)R₇, or -S(O)₂R₇;

each halo is independently -F, -Cl, -Br, or -I;

5 m is 0 or 1;

n is an integer ranging from 0 to 3;

o is an integer ranging from 0 to 4;

p is an integer ranging from 0 to 2;

q is an integer ranging from 0 to 6;

10 r is an integer ranging from 0 to 5;

s is an integer ranging from 0 to 4; and

t is an integer ranging from 0 to 2.

A compound of formula (I), (Ia), (Ib), (Ic), (II), (IIa), (III), (IIIa), (IIIb), (IIIc), (IV), (IVa), (V), (VI), or (VII), or a pharmaceutically acceptable salt thereof (a
15 “Cyanoiminopiperazine Compound”) is useful for treating or preventing pain, UI, an ulcer, IBD, IBS, an addictive disorder, Parkinson’s disease, parkinsonism, anxiety, epilepsy, stroke, a seizure, a pruritic condition, psychosis, a cognitive disorder, a memory deficit, restricted brain function, Huntington’s chorea, ALS, dementia, retinopathy, a muscle spasm, a migraine, vomiting, dyskinesia, or depression (each being a “Condition”) in an animal.

20 The invention also relates to compositions comprising an effective amount of a Cyanoiminopiperazine Compound and a pharmaceutically acceptable carrier or excipient. The compositions are useful for treating or preventing a Condition in an animal.

The invention further relates to methods for treating a Condition, comprising administering to an animal in need thereof an effective amount of a Cyanoiminopiperazine
25 Compound.

The invention further relates to methods for preventing a Condition, comprising administering to an animal in need thereof an effective amount of a Cyanoiminopiperazine Compound.

The invention still further relates to methods for inhibiting Vanilloid Receptor
30 1 (“VR1”) function in a cell, comprising contacting a cell capable of expressing VR1 with an effective amount of a Cyanoiminopiperazine Compound.

The invention still further relates to methods for inhibiting mGluR5 function in a cell, comprising contacting a cell capable of expressing mGluR5 with an effective amount of a Cyanoiminopiperazine Compound.

The invention still further relates to methods for inhibiting metabotropic glutamate receptor 1 (“mGluR1”) function in a cell, comprising contacting a cell capable of expressing mGluR1 with an effective amount of a Cyanoiminopiperazine Compound.

The invention still further relates to a method for preparing a composition, comprising the step of admixing a Cyanoiminopiperazine Compound and a pharmaceutically acceptable carrier or excipient.

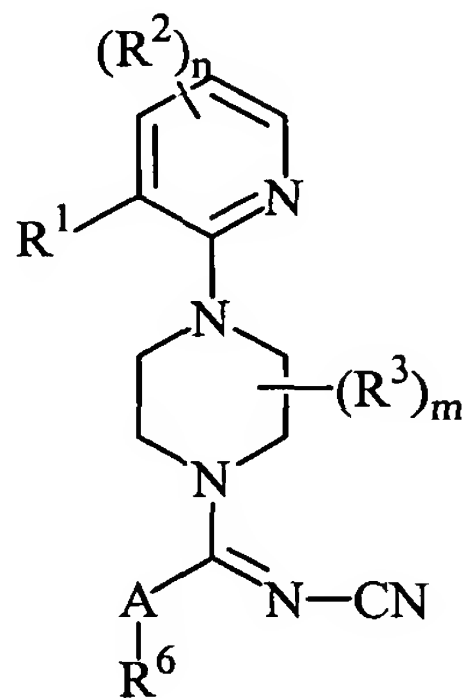
The invention still further relates to a kit comprising a container containing an effective amount of a Cyanoiminopiperazine Compound.

The present invention may be understood more fully by reference to the following detailed description and illustrative examples, which are intended to exemplify non-limiting embodiments of the invention.

4. DETAILED DESCRIPTION OF THE INVENTION

4.1 CYANOIMINOPIPERAZINE COMPOUNDS OF FORMULA (I)

As stated above, the present invention encompasses compounds of Formula (I)



(I)

and pharmaceutically acceptable salts thereof, where A, R¹, R², R³, R⁶, n, and m are defined above for the Cyanoiminopiperazine Compounds of formula (I).

In one embodiment n is 0.

In another embodiment, n is 1.

- In another embodiment, n is 2.
- In another embodiment, n is 3.
- In another embodiment, m is 0.
- In another embodiment, m is 1.
- 5 In another embodiment, m is 2.
- In another embodiment, A is -N((C₁-C₆)alkyl)-.
- In another embodiment, A is -N(O(C₁-C₆)alkyl)-.
- In another embodiment, A is -O-.
- In another embodiment, A is -S-.
- 10 In another embodiment, R¹ is halo.
- In another embodiment, R¹ is -Cl.
- In another embodiment, R¹ is -Br.
- In another embodiment, R¹ is -I.
- In another embodiment, R¹ is -F.
- 15 In another embodiment, R¹ is -CH₃.
- In another embodiment, n is 1 and R² is -halo, -CN, -OH, -NO₂, or -NH₂.
- In another embodiment, n is 1 and R² is -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(C₃-C₇)heterocycle, or -(C₇-C₁₀)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R⁵ groups.
- 20 In another embodiment, n is 1 and R² is -phenyl, -naphthyl, -(C₁₄)aryl, or -(C₅-C₁₀)heteroaryl, each of which is unsubstituted or substituted with one or more R⁷ groups;
- In another embodiment, m is 1 and R³ is -halo, -CN, -OH, -NO₂, or -NH₂.
- 25 In another embodiment, m is 1 and R³ is -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(C₃-C₇)heterocycle, or -(C₇-C₁₀)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R⁵ groups.
- 30 In another embodiment, m is 1 and R³ is -phenyl, -naphthyl, -(C₁₄)aryl or -(C₅-C₁₀)heteroaryl, each of which is unsubstituted or substituted with one or more R⁷ groups.

In another embodiment, R⁶ is -phenyl, -naphthyl, -(C₃-C₈)cycloalkyl, -(C₁₄)aryl, or -(C₅-C₁₀)heteroaryl, each of which is unsubstituted or substituted with one or more R⁷ groups.

In another embodiment, R⁶ is -phenyl.

5 In another embodiment, m is 1 and R³ is -CH₃.

In another embodiment, m is 1, R³ is -CH₃, and the carbon atom to which the -R³ is attached is in the (R)-configuration.

In another embodiment, m is 1, R³ is -CH₃, and the carbon atom to which the -R³ is attached is in the (S)-configuration.

10 In one embodiment, n and m are 0 and R⁶ is -phenyl. In another embodiment, n is 0, m is 1, R³ is methyl, and R⁶ is phenyl. In another embodiment, the -phenyl is substituted with a -(C₁-C₆) alkyl group. In another embodiment, the -(C₁-C₆) alkyl group is substituted at the 4-position of the -phenyl. In another embodiment, the -(C₁-C₆) alkyl group is a *t*-butyl group substituted at 4-position of the -phenyl. In another embodiment, the -(C₁-
15 C₆) alkyl group is an *iso*-propyl group substituted at the 4-position of the -phenyl.

In another embodiment, R¹ is -CF₃ or -CHF₂.

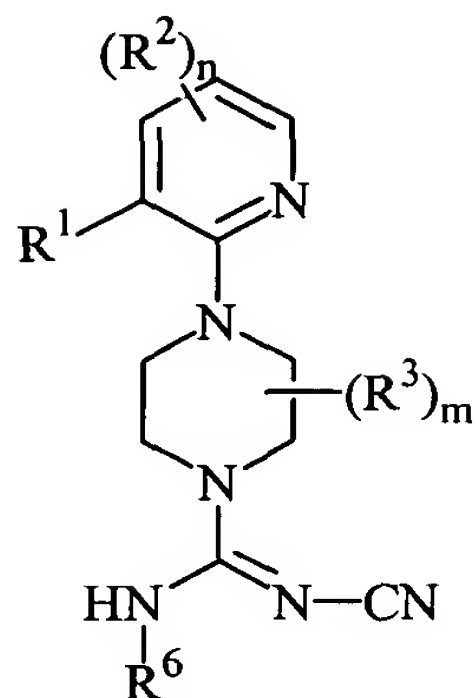
In another embodiment, n and m are 0 and R⁶ is -phenyl substituted at its 4-position with a -CF₃ group.

In another embodiment, n and m are 0, R¹ is -halo or methyl; and R⁶ is
20 -phenyl. In one embodiment, -halo is -Cl. In another embodiment, the -phenyl is substituted with a -(C₁-C₆) alkyl group. In another embodiment, the -(C₁-C₆) alkyl group is substituted at the 4-position of the -phenyl. In another embodiment, the -(C₁-C₆) alkyl group is a *t*-butyl group or an *iso*-propyl group substituted at the 4-position of the -phenyl.

In another embodiment, n and m are 0, R¹ is -halo or methyl; and R⁶ is -phenyl
25 substituted with -CF₃. In another embodiment, -halo is -Cl. In another embodiment, the -CF₃ is substituted at the 4-position of the -phenyl. In another embodiment, -halo is -Cl and the -CF₃ is substituted at the 4-position of the -phenyl.

4.2 CYANOIMINOPIPERAZINE COMPOUNDS OF FORMULA (IA)

30 The present invention also encompasses compounds of formula (Ia)



(Ia)

and pharmaceutically acceptable salts thereof, wherein R¹, R², R³, R⁶, n, and m are defined above for the Cyanoiminopiperazine Compounds of formula (Ia).

In one embodiment, R¹ is -halo.

In another embodiment, R¹ is -Cl.

In another embodiment, R¹ is -Br.

In another embodiment, R¹ is -I.

In another embodiment, R¹ is -F.

In another embodiment, R¹ is -CH₃.

In another embodiment, n is 1 and R² is -halo, -CN, -OH, -NO₂, or -NH₂.

In another embodiment, n is 1 and R² is -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(C₃-C₇)heterocycle, or -(C₇-C₁₀)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R⁵ groups.

In another embodiment, n is 1 and R² is -phenyl, -naphthyl, -(C₁₄)aryl, or -(C₅-C₁₀)heteroaryl, each of which is unsubstituted or substituted with one or more R⁷ groups.

In another embodiment, m is 1 and R³ is -halo, -CN, -OH, -NO₂, or -NH₂.

In another embodiment, m is 1 and R³ is -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(C₃-C₇)heterocycle, or -

(C₇-C₁₀)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R⁵ groups.

In another embodiment, m is 1 and R³ is -phenyl, -naphthyl, -(C₁₄)aryl or -(C₅-C₁₀)heteroaryl, each of which is unsubstituted or substituted with one or more R⁷ groups.

5 In another embodiment, m is 1 and R³ is -CH₃.

In another embodiment, m is 1, R³ is -CH₃, and the carbon atom to which the -R³ is attached is in the (R)-configuration.

In another embodiment, m is 1, R³ is -CH₃, and the carbon atom to which the -R³ is attached is in the (S)-configuration.

10 In another embodiment, R⁶ is -naphthyl, -(C₁₄)aryl, or -(C₃-C₈)cycloalkyl each of which is unsubstituted or substituted with one or more R⁷ groups.

In another embodiment, R⁶ is pyridyl, furyl, benzofuranyl, thiophenyl, benzothiophenyl, quinolinyl, indolyl, oxazolyl, benzoxazolyl, imidazolyl, benzimidazolyl, thiazolyl, benzothiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiadiazolyl, triazinyl, cinnolyl, phthalazinyl, or quinazolinyl, each of which is substituted with one or more R⁷ groups.

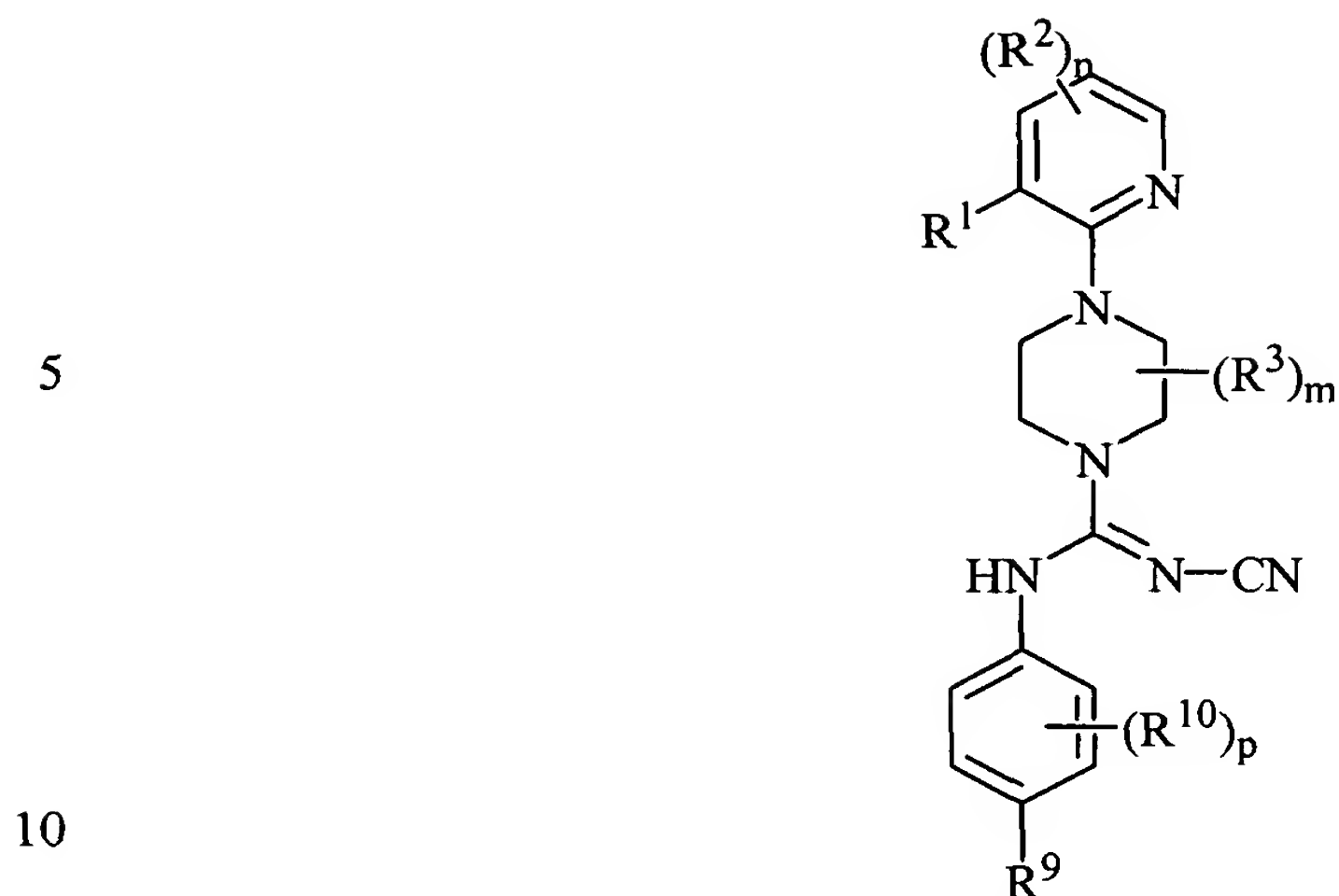
15 In another embodiment, R⁶ is pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, or thiadiazolyl.

20 **4.3 CYANOIMINOPIPERAZINE COMPOUNDS OF FORMULA (IB)**

The present invention encompasses compounds having the formula (Ib):

25

30



(Ib)

and pharmaceutically acceptable salts thereof, wherein R¹, R², R³, R⁹, R¹⁰, n, m, p and halo are defined above for the Cyanoiminopiperazine Compounds of formula (Ib).

- 15 In one embodiment, n is 0.
 In another embodiment, n is 1.
 In another embodiment, n is 2.
 In another embodiment, m is 0.
 In another embodiment m is 1.
 20 In another embodiment, m is 2.
 In another embodiment, R¹ is -halo.
 In another embodiment, R¹ is -Cl.
 In another embodiment, R¹ is -Br.
 In another embodiment, R¹ is -I.
 25 In another embodiment, R¹ is -F.
 In another embodiment, R¹ is -CH₃.
 In one embodiment, n is 1 and R² is -halo, -CN, -OH, -NO₂, or -NH₂.
 In another embodiment, n is 1 and R² is -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-
 C₁₀)alkynyl, -(C₃-C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-
 30 C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(C₃-C₇)heterocycle, or

-(C₇-C₁₀)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R⁵ groups.

In another embodiment, n is 1 and R² is -phenyl, -naphthyl, -(C₁₄)aryl, or -(C₅-C₁₀)heteroaryl, each of which is unsubstituted or substituted with one or more R⁷ groups.

In another embodiment, m is 1 and R³ is -halo, -CN, -OH, -NO₂, or -NH₂.

In another embodiment, m is 1 and R³ is -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(C₃-C₇)heterocycle, or -(C₇-C₁₀)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R⁵ groups.

In another embodiment, m is 1 and R³ is -phenyl, -naphthyl, -(C₁₄)aryl or -(C₅-C₁₀)heteroaryl, each of which is unsubstituted or substituted with one or more R⁷ groups.

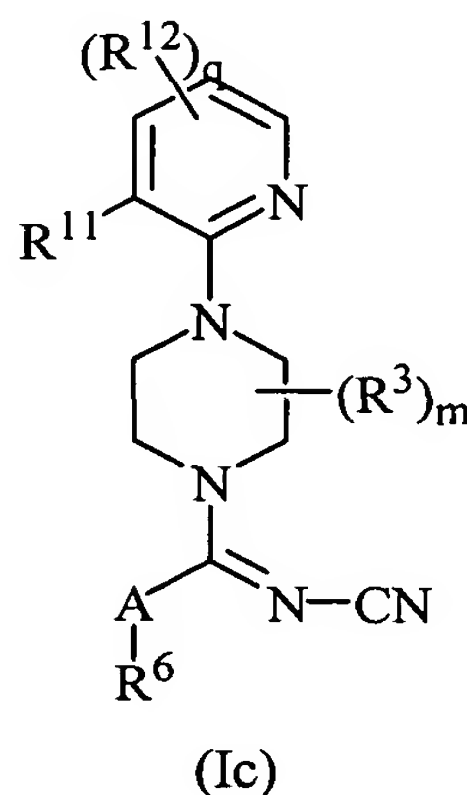
In another embodiment, m is 1 and R³ is -CH₃.

In another embodiment, m is 1, R³ is -CH₃, and the carbon atom to which the -R³ is attached is in the (R)-configuration.

In another embodiment, m is 1, R³ is -CH₃, and the carbon atom to which the -R³ is attached is in the (S)-configuration.

4.4 CYANOIMINOPIPERAZINE COMPOUNDS OF FORMULA (Ic)

The present invention encompasses compounds having the formula (Ic):



and pharmaceutically acceptable salts thereof, wherein A, R³, R⁶, R¹¹, R¹², m, and q are defined above for the Cyanoiminopiperazine Compounds of formula (Ic).

In one embodiment, m is 0.

In another embodiment, m is 1.

5 In another embodiment, m is 2.

In another embodiment, q is 0.

In another embodiment, q is 1.

In another embodiment, q is 2.

In another embodiment, q is 3.

10 In another embodiment, A is -N((C₁-C₆)alkyl)-.

In another embodiment, A is -N(O(C₁-C₆)alkyl)-.

In another embodiment, A is -O-.

In another embodiment, A is -S-.

In another embodiment, m is 1 and R³ is -halo, -CN, -OH, -NO₂, or -NH₂; or

15 In another embodiment, m is 1 and R³ is -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(C₃-C₇)heterocycle, or -(C₇-C₁₀)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R⁵ groups.

20 In another embodiment, m is 1 and R³ is -phenyl, -naphthyl, -(C₁₄)aryl or -(C₅-C₁₀)heteroaryl, each of which is unsubstituted or substituted with one or more R⁷ groups.

In another embodiment, m is 1 and R³ is -CH₃.

In another embodiment, m is 1, R³ is -CH₃, and the carbon atom to which the -R³ is attached is in the (R)-configuration.

25 In another embodiment, m is 1, R³ is -CH₃, and the carbon atom to which the -R³ is attached is in the (S)-configuration.

In another embodiment, R⁶ is -phenyl, -naphthyl, -(C₃-C₈)cycloalkyl, -(C₁₄)aryl, or -(C₅-C₁₀)heteroaryl, each of which is unsubstituted or substituted with one or more R⁷ groups.

30 In another embodiment, R⁶ is -phenyl.

In another embodiment, R^{11} is -hydrogen, -halo, -CH₃, -NO₂, -CN, -OH, -OCH₃, -NH₂, -C(halo)₃, -CH(halo)₂, or -CH₂(halo).

In another embodiment, R^{11} is -halo.

In another embodiment, R^{11} is -Cl.

5 In another embodiment, R^{11} is -Br.

In another embodiment, R^{11} is -F.

In another embodiment, R^{11} is -I.

In another embodiment, R^{11} is -CH₃.

In another embodiment, q is 1 and R^{12} is -halo, -CN, -OH, -NO₂, or -NH₂.

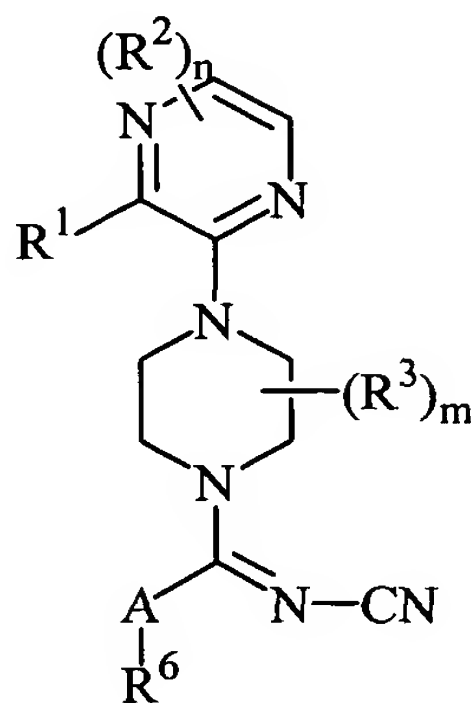
10 In another embodiment, q is 1 and R^{12} is -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(C₃-C₇)heterocycle, or -(C₇-C₁₀)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R^5 groups.

15 In one embodiment, q is 1 and R^{12} is -phenyl, -naphthyl, -(C₁₄)aryl, or -(C₅-C₁₀)heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups.

4.5 CYANOIMINOPIPERAZINE COMPOUNDS OF FORMULA (II)

The present invention also encompasses compounds of formula (II)

20



25

(II)

and pharmaceutically acceptable salts thereof, wherein A, R^1 , R^2 , R^3 , R^6 , n, and m are defined
30 above for the Cyanoiminopiperazine Compounds of formula (II).

In one embodiment, n is 0.

In another embodiment, n is 1.

In another embodiment, n is 2.

In another embodiment, m is 0.

In another embodiment, m is 1.

5 In another embodiment, m is 2.

In another embodiment, R¹ is -halo.

In another embodiment, R¹ is -Cl.

In another embodiment, R¹ is -Br.

In another embodiment, R¹ is -I.

10 In another embodiment, R¹ is -F.

In another embodiment, R¹ is -CH₃.

In another embodiment, A is -NH-.

In another embodiment, A is -N((C₁-C₆)alkyl)-.

In another embodiment, A is -N(O(C₁-C₆)alkyl)-.

15 In another embodiment, A is -O-.

In another embodiment, A is -S-.

In another embodiment, n is 1 and R² is -halo, -CN, -OH, -NO₂, or -NH₂.

In another embodiment, n is 1 and R² is -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(C₃-C₇)heterocycle, or -(C₇-C₁₀)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R⁵ groups.

20 In another embodiment, n is 1 and R² is -phenyl, -naphthyl, -(C₁₄)aryl, or -(C₅-C₁₀)heteroaryl, each of which is unsubstituted or substituted with one or more R⁷ groups.

25 In another embodiment, m is 1 and R³ is -halo, -CN, -OH, -NO₂, or -NH₂.

In another embodiment, m is 1 and R³ is -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(C₃-C₇)heterocycle, or -(C₇-C₁₀)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R⁵ groups.

30 groups.

In another embodiment, m is 1 and R³ is -phenyl, -naphthyl, -(C₁₄)aryl or -(C₅-C₁₀)heteroaryl, each of which is unsubstituted or substituted with one or more R⁷ groups.

In another embodiment, m is 1 and R³ is -CH₃.

In another embodiment, m is 1, R³ is -CH₃, and the carbon atom to which the -
5 R³ is attached is in the (R)-configuration.

In another embodiment, m is 1, R³ is -CH₃, and the carbon atom to which the -
R³ is attached is in the (S)-configuration.

In another embodiment, R⁶ is -phenyl, -naphthyl, -(C₃-C₈)cycloalkyl, -(C₁₄)aryl,
or -(C₅-C₁₀)heteroaryl, each of which is unsubstituted or substituted with one or more R⁷
10 groups.

In another embodiment, R⁶ is -phenyl.

In one embodiment, n and m are 0 and R⁶ is -phenyl. In another embodiment,
n is 0, m is 1, R³ is methyl, and R⁶ is phenyl. In another embodiment, the -phenyl is
substituted with a -(C₁-C₆) alkyl group. In another embodiment, the -(C₁-C₆) alkyl group is
15 substituted at the 4-position of the -phenyl. In another embodiment, the -(C₁-C₆) alkyl group
is a *t*-butyl group substituted at 4-position of the -phenyl. In another embodiment, the -(C₁-
C₆) alkyl group is an *iso*-propyl group substituted at the 4-position of the -phenyl.

In another embodiment, R¹ is -CF₃ or -CHF₂.

In another embodiment, n and m are 0 and R⁶ is -phenyl substituted at its 4-
20 position with a -CF₃ group.

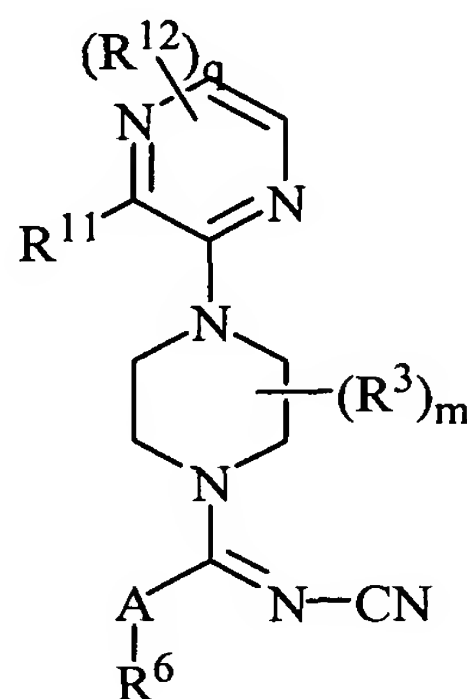
In another embodiment, n and m are 0, R¹ is -halo or methyl; and R⁶ is
-phenyl. In one embodiment, -halo is -Cl. In another embodiment, the -phenyl is substituted
with a -(C₁-C₆) alkyl group. In another embodiment, the -(C₁-C₆) alkyl group is substituted at
the 4-position of the -phenyl. In another embodiment, the -(C₁-C₆) alkyl group is a *t*-butyl
25 group or an *iso*-propyl group substituted at the 4-position of the -phenyl.

In another embodiment, n and m are 0, R¹ is -halo or methyl; and R⁶ is -phenyl
substituted with -CF₃. In another embodiment, -halo is -Cl. In another embodiment, the -CF₃
is substituted at the 4-position of the -phenyl. In another embodiment, -halo is -Cl and the
-CF₃ is substituted at the 4-position of the -phenyl.

30

4.6 CYANOIMINOPIPERAZINE COMPOUNDS OF FORMULA (IIa)

The present invention also encompasses compounds having the formula (IIa):



(IIa)

and pharmaceutically acceptable salts thereof, wherein A , R^3 , R^6 , R^{11} , R^{12} , m , and q are defined above for the Cyanoiminopiperazine Compounds of formula (IIa).

In one embodiment, q is 0.

In another embodiment q is 1.

In another embodiment q is 2.

In one embodiment, m is 0.

In another embodiment, m is 1.

In another embodiment, m is 2.

In another embodiment, A is $-N((C_1-C_6)\text{alkyl})-$.

In another embodiment, A is $-N(O(C_1-C_6)\text{alkyl})-$.

In another embodiment, A is $-O-$.

In another embodiment, A is $-S-$.

In another embodiment, m is 1 and R^3 is $-\text{halo}$, $-\text{CN}$, $-\text{OH}$, $-\text{NO}_2$, or $-\text{NH}_2$.

In another embodiment, m is 1 and R^3 is $-(C_1-C_{10})\text{alkyl}$, $-(C_2-C_{10})\text{alkenyl}$, $-(C_2-C_{10})\text{alkynyl}$, $-(C_3-C_{10})\text{cycloalkyl}$, $-(C_8-C_{14})\text{bicycloalkyl}$, $-(C_8-C_{14})\text{tricycloalkyl}$, $-(C_5-C_{10})\text{cycloalkenyl}$, $-(C_8-C_{14})\text{bicycloalkenyl}$, $-(C_8-C_{14})\text{tricycloalkenyl}$, $-(C_3-C_7)\text{heterocycle}$, or $-(C_7-C_{10})\text{bicycloheterocycle}$, each of which is unsubstituted or substituted with one or more R^5 groups.

In another embodiment, m is 1 and R^3 is $-\text{phenyl}$, $-\text{naphthyl}$, $-(C_{14})\text{aryl}$ or $-(C_5-C_{10})\text{heteroaryl}$, each of which is unsubstituted or substituted with one or more R^7 groups.

In another embodiment, m is 1 and R³ is -CH₃.

In another embodiment, m is 1, R³ is -CH₃, and the carbon atom to which the - R³ is attached is in the (R)-configuration.

In another embodiment, m is 1, R³ is -CH₃, and the carbon atom to which the -
5 R³ is attached is in the (R)-configuration.

In another embodiment, R⁶ is -phenyl, -naphthyl, -(C₃-C₈)cycloalkyl, -(C₁₄)aryl, or -(C₅-C₁₀)heteroaryl, each of which is unsubstituted or substituted with one or more R⁷ groups.

In another embodiment, R⁶ is -phenyl.

10 In another embodiment, R¹¹ is -hydrogen, -halo, -CH₃, -NO₂, -CN, -OH, -OCH₃, -NH₂, -C(halo)₃, -CH(halo)₂, or -CH₂(halo).

In another embodiment, R¹¹ is -halo.

In another embodiment, R¹¹ is -Cl.

In another embodiment, R¹¹ is -Br.

15 In another embodiment, R¹¹ is -F.

In another embodiment, R¹¹ is -I.

In another embodiment, R¹¹ is -CH₃.

In another embodiment, q is 1 and R¹² is -halo, -CN, -OH, -NO₂, or -NH₂.

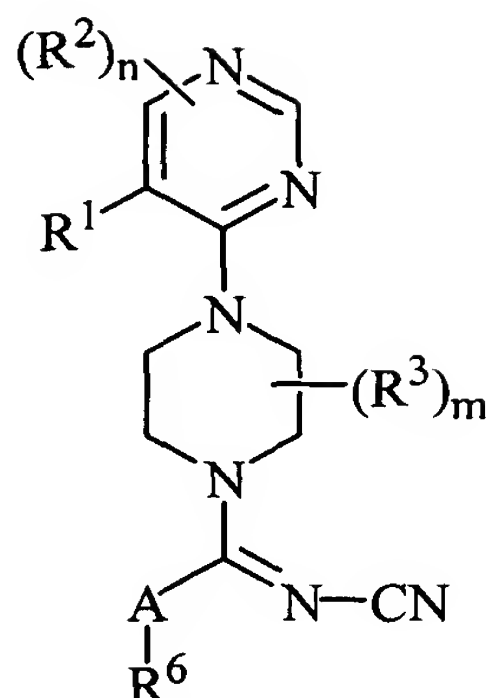
In another embodiment, q is 1 and R¹² is -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-
20 C₁₀)alkynyl, -(C₃-C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(C₃-C₇)heterocycle, or -(C₇-C₁₀)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R⁵ groups.

In another embodiment, q is 1 and R¹² is -phenyl, -naphthyl, -(C₁₄)aryl, or -(C₅-
25 C₁₀)heteroaryl, each of which is unsubstituted or substituted with one or more R⁷ groups.

4.7 CYANOIMINOPIPERAZINE COMPOUNDS OF FORMULA (III)

The present invention also encompasses compounds of formula (III)

5



(III)

10 and pharmaceutically acceptable salts thereof, wherein $A, R^1, R^2, R^3, R^6, m,$ and n are defined above for the Cyanoiminopiperazine Compounds of formula (III).

In one embodiment, n is 0.

In one embodiment, n is 1.

In one embodiment, n is 2.

15

In one embodiment, m is 0.

In one embodiment, m is 1.

In one embodiment, m is 2.

In another embodiment, A is $-N((C_1-C_6)\text{alkyl})-$.

In another embodiment, A is $-N(O(C_1-C_6)\text{alkyl})-$.

20

In one embodiment, A is $-O-$.

In one embodiment, A is $-S-$.

In one embodiment, R^1 is $-\text{halo}$.

In one embodiment, R^1 is $-\text{Cl}$.

In one embodiment, R^1 is $-\text{Br}$.

25

In one embodiment, R^1 is $-\text{I}$.

In one embodiment, R^1 is $-\text{F}$.

In one embodiment, R^1 is $-\text{CH}_3$.

In one embodiment, n is 1 and R^2 is $-\text{halo}, -\text{CN}, -\text{OH}, -\text{NO}_2,$ or $-\text{NH}_2$.

In one embodiment, n is 1 and R^2 is $-(C_1-C_{10})\text{alkyl}, -(C_2-C_{10})\text{alkenyl}, -(C_2-$

30 $C_{10})\text{alkynyl}, -(C_3-C_{10})\text{cycloalkyl}, -(C_8-C_{14})\text{bicycloalkyl}, -(C_8-C_{14})\text{tricycloalkyl}, -(C_5-C_{10})\text{cycloalkenyl}, -(C_8-C_{14})\text{bicycloalkenyl}, -(C_8-C_{14})\text{tricycloalkenyl}, -(C_3-C_7)\text{heterocycle},$ or $-$

(C₇-C₁₀)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R⁵ groups.

In one embodiment, n is 1 and R² is -phenyl, -naphthyl, -(C₁₄)aryl, or -(C₅-C₁₀)heteroaryl, each of which is unsubstituted or substituted with one or more R⁷ groups.

5 In one embodiment, m is 1 and R³ is -halo, -CN, -OH, -NO₂, or -NH₂.

In one embodiment, m is 1 and R³ is -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(C₃-C₇)heterocycle, or -(C₇-C₁₀)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R⁵ groups.

In one embodiment, m is 1 and R³ is -phenyl, -naphthyl, -(C₁₄)aryl or -(C₅-C₁₀)heteroaryl, each of which is unsubstituted or substituted with one or more R⁷ groups.

In another embodiment, m is 1 and R³ is -CH₃.

In another embodiment, m is 1, R³ is -CH₃, and the carbon atom to which the -R³ is attached is in the (R)-configuration.

In another embodiment, m is 1, R³ is -CH₃, and the carbon atom to which the -R³ is attached is in the (S)-configuration.

In one embodiment, R⁶ is -phenyl, -naphthyl, -(C₃-C₈)cycloalkyl, -(C₁₄)aryl, or -(C₅-C₁₀)heteroaryl, each of which is unsubstituted or substituted with one or more R⁷ groups.

20 In one embodiment, R⁶ is -phenyl.

In one embodiment, n and m are 0 and R⁶ is -phenyl. In another embodiment, n is 0, m is 1, R³ is methyl, and R⁶ is phenyl. In another embodiment, the -phenyl is substituted with a -(C₁-C₆) alkyl group. In another embodiment, the -(C₁-C₆) alkyl group is substituted at the 4-position of the -phenyl. In another embodiment, the -(C₁-C₆) alkyl group is a *t*-butyl group substituted at 4-position of the -phenyl. In another embodiment, the -(C₁-C₆) alkyl group is an *iso*-propyl group substituted at the 4-position of the -phenyl.

In another embodiment, R¹ is -CF₃ or -CHF₂.

In another embodiment, n and m are 0 and R⁶ is -phenyl substituted at its 4-position with a -CF₃ group.

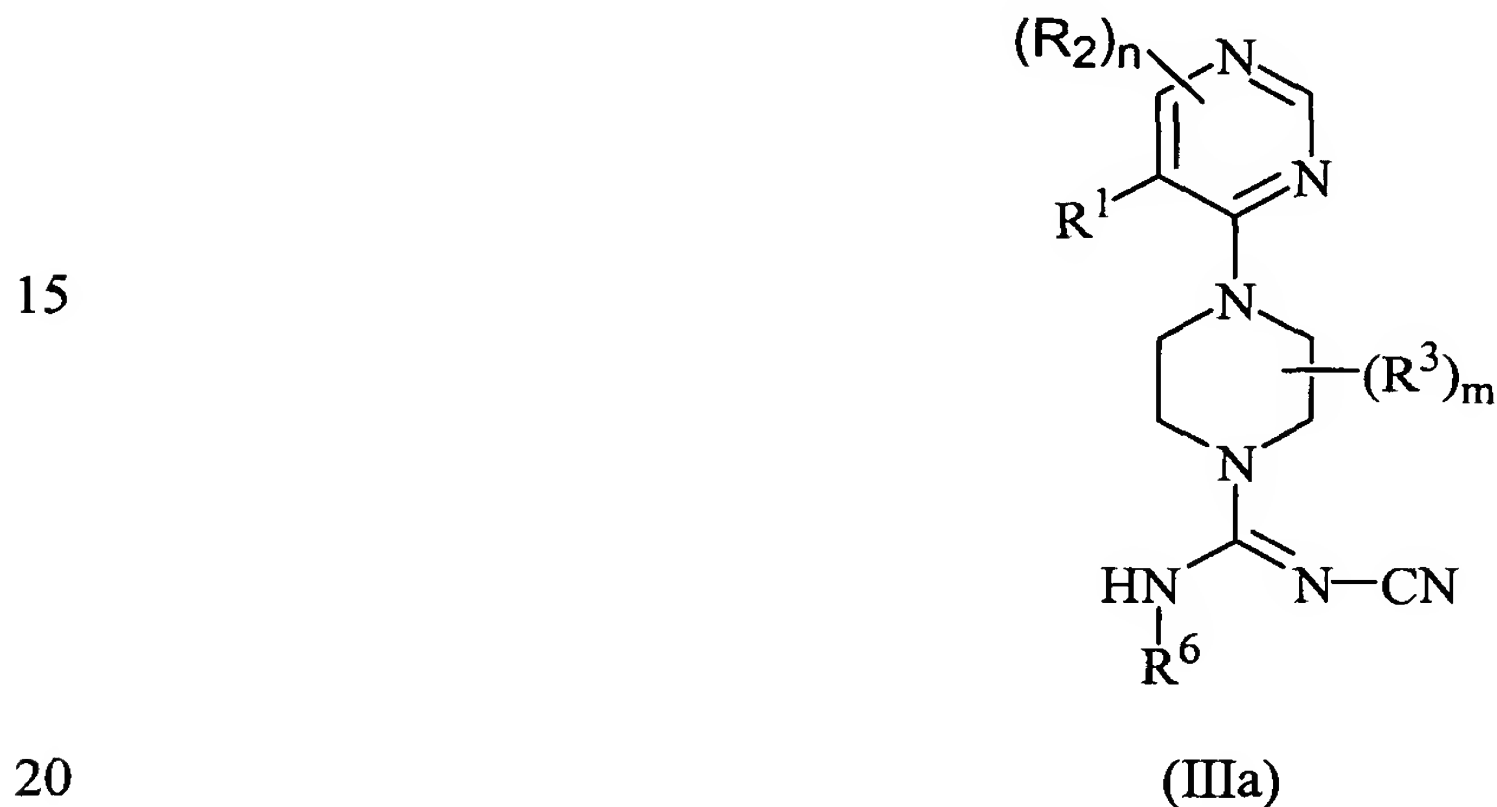
30 In another embodiment, n and m are 0, R¹ is -halo or methyl; and R⁶ is

-phenyl. In one embodiment, -halo is -Cl. In another embodiment, the -phenyl is substituted with a $-(C_1-C_6)$ alkyl group. In another embodiment, the $-(C_1-C_6)$ alkyl group is substituted at the 4-position of the -phenyl. In another embodiment, the $-(C_1-C_6)$ alkyl group is a *t*-butyl group or an *iso*-propyl group substituted at the 4-position of the -phenyl.

5 In another embodiment, *n* and *m* are 0, R^1 is -halo or methyl; and R^6 is -phenyl substituted with $-CF_3$. In another embodiment, -halo is -Cl. In another embodiment, the $-CF_3$ is substituted at the 4-position of the -phenyl. In another embodiment, -halo is -Cl and the $-CF_3$ is substituted at the 4-position of the -phenyl.

10 4.8 CYANOIMINOPIPERAZINE COMPOUNDS OF FORMULA (IIIa)

The present invention also encompasses compounds of formula (IIIa)



and pharmaceutically acceptable salts thereof, wherein R^1 , R^2 , R^3 , R^6 , *n*, and *m* are defined above for the Cyanoiminopiperazine Compounds of formula (IIIa).

In one embodiment, *n* is 0.

In another embodiment, *n* is 1.

25 In another embodiment, *n* is 2.

In another embodiment, *m* is 0.

In another embodiment, *m* is 1.

In another embodiment, *m* is 2.

In another embodiment, R^1 is -halo.

30 In another embodiment, R^1 is -Cl.

In another embodiment, R^1 is -Br.

In another embodiment, R¹ is -I.

In another embodiment, R¹ is -F.

In another embodiment, R¹ is -CH₃.

In another embodiment, n is 1 and R² is -halo, -CN, -OH, -NO₂, or -NH₂;

5 In another embodiment, n is 1 and R² is -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(C₃-C₇)heterocycle, or -(C₇-C₁₀)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R⁵ groups; or

10 In another embodiment, n is 1 and R² is -phenyl, -naphthyl, -(C₁₄)aryl, or -(C₅-C₁₀)heteroaryl, each of which is unsubstituted or substituted with one or more R⁷ groups;

In another embodiment, m is 1 and R³ is -halo, -CN, -OH, -NO₂, or -NH₂; or

In another embodiment, m is 1 and R³ is -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(C₃-C₇)heterocycle, or -(C₇-C₁₀)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R⁵ groups; or

In another embodiment, m is 1 and R³ is -phenyl, -naphthyl, -(C₁₄)aryl or -(C₅-C₁₀)heteroaryl, each of which is unsubstituted or substituted with one or more R⁷ groups.

20 In another embodiment, m is 1 and R³ is -CH₃.

In another embodiment, m is 1, R³ is -CH₃, and the carbon atom to which the -R³ is attached is in the (R)-configuration.

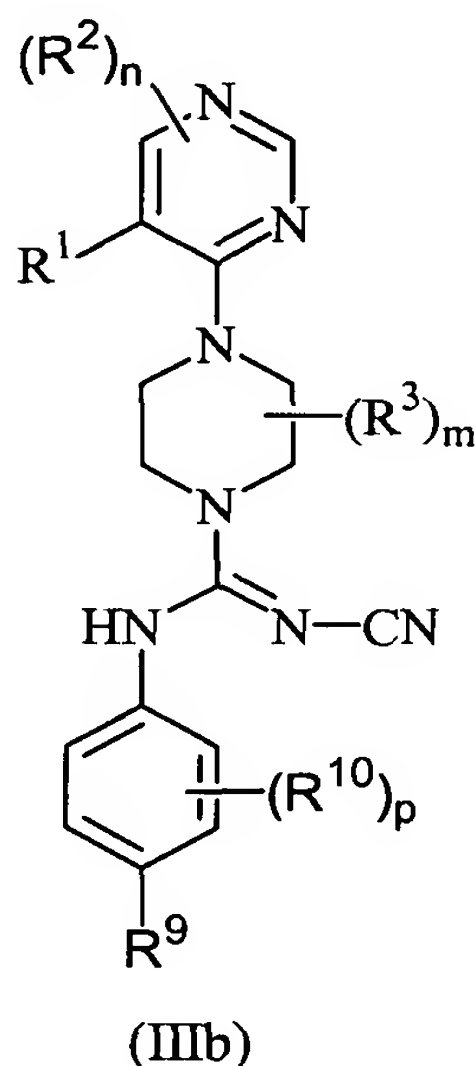
In another embodiment, m is 1, R³ is -CH₃, and the carbon atom to which the -R³ is attached is in the (S)-configuration.

25 In another embodiment, R⁶ is -naphthyl, -(C₁₄)aryl, or -(C₃-C₈)cycloalkyl each of which is unsubstituted or substituted with one or more R⁷ groups.

In another embodiment, R⁶ is pyridyl, furyl, benzofuranyl, thiophenyl, benzothiophenyl, quinoliny, indolyl, oxazolyl, benzoxazolyl, imidazolyl, benzimidazolyl, thiazolyl, benzothiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiadiazolyl, triazinyl, cinnoliny, phthalazinyl, or quinazolinyl, each of which is substituted with one or more R⁷ groups.

4.9 CYANOIMINOPIPERAZINE COMPOUNDS OF FORMULA (IIIb)

The present invention encompasses compounds having the formula (IIIb):



and pharmaceutically acceptable salts thereof, wherein R^1 , R^2 , R^3 , R^9 , R^{10} , n , m , and p are defined above for the Cyanoiminopiperazine Compounds of formula (IIIb).

In one embodiment, n is 0.

In another embodiment, n is 1.

20 In another embodiment, n is 2.

In one embodiment, m is 0.

In another embodiment, m is 1.

In another embodiment, m is 2.

In one embodiment, p is 0.

25 In another embodiment, p is 1.

In another embodiment, p is 2.

In another embodiment, p is 3.

In another embodiment, p is 4.

In another embodiment, R^1 is -halo.

30 In another embodiment, R^1 is -Cl.

In another embodiment, R^1 is -Br.

In another embodiment, R¹ is -I.

In another embodiment, R¹ is -F.

In another embodiment, R¹ is -CH₃.

In another embodiment, n is 1 and R² is -halo, -CN, -OH, -NO₂, or -NH₂.

5 In another embodiment, n is 1 and R² is -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(C₃-C₇)heterocycle, or -(C₇-C₁₀)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R⁵ groups.

10 In another embodiment, n is 1 and R² is -phenyl, -naphthyl, -(C₁₄)aryl, or -(C₅-C₁₀)heteroaryl, each of which is unsubstituted or substituted with one or more R⁷ groups.

In another embodiment, m is 1 and R³ is -halo, -CN, -OH, -NO₂, or -NH₂.

In another embodiment, m is 1 and R³ is -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(C₃-C₇)heterocycle, or -(C₇-C₁₀)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R⁵ groups.

In another embodiment, m is 1 and R³ is -phenyl, -naphthyl, -(C₁₄)aryl or -(C₅-C₁₀)heteroaryl, each of which is unsubstituted or substituted with one or more R⁷ groups.

20 In another embodiment, m is 1 and R³ is -CH₃.

In another embodiment, m is 1, R³ is -CH₃, and the carbon atom to which the -R³ is attached is in the (R)-configuration.

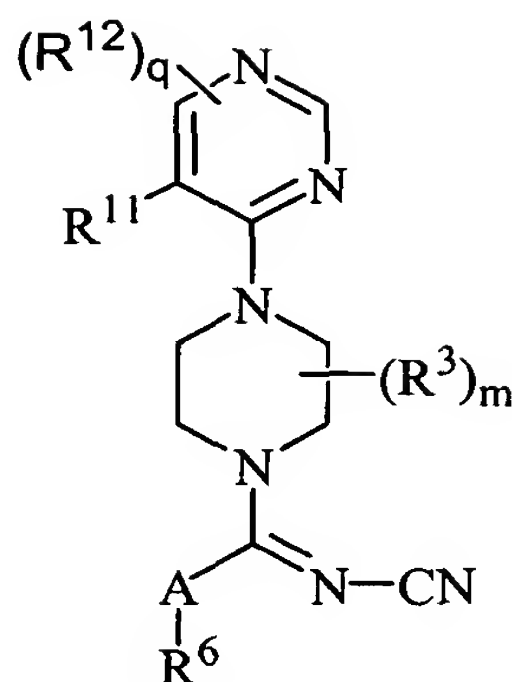
In another embodiment, m is 1, R³ is -CH₃, and the carbon atom to which the -R³ is attached is in the (S)-configuration.

25

4.10 CYANOIMINOPIPERAZINE COMPOUNDS OF FORMULA (IIIC)

The present invention encompasses compounds having the formula (IIIC):

5



(IIIc)

10 and pharmaceutically acceptable salts thereof, wherein A, R³, R⁶, R¹¹, R¹², m, and q are defined above for the Cyanoiminopiperazine Compounds of formula (IIIc).

In one embodiment, q is 0.

In another embodiment, q is 1.

In another embodiment, q is 2.

15

In one embodiment, m is 0.

In another embodiment, m is 1.

In another embodiment, m is 2.

In another embodiment, A is -N((C₁-C₆)alkyl)-.

In another embodiment, A is -N(O(C₁-C₆)alkyl)-.

20

In another embodiment, A is -O-.

In another embodiment, A is -S-.

In another embodiment, m is 1 and R³ is -halo, -CN, -OH, -NO₂, or -NH₂.

In another embodiment, m is 1 and R³ is -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(C₃-C₇)heterocycle, or -(C₇-C₁₀)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R⁵ groups.

25

In another embodiment, m is 1 and R³ is -phenyl, -naphthyl, -(C₁₄)aryl or -(C₅-C₁₀)heteroaryl, each of which is unsubstituted or substituted with one or more R⁷ groups.

30

In another embodiment, m is 1 and R³ is -CH₃.

In another embodiment, m is 1, R³ is -CH₃, and the carbon atom to which the -R³ is attached is in the (R)-configuration.

In another embodiment, m is 1, R³ is -CH₃, and the carbon atom to which the -R³ is attached is in the (S)-configuration.

5 In another embodiment, R⁶ is -phenyl, -naphthyl, -(C₃-C₈)cycloalkyl, -(C₁₄)aryl, or -(C₅-C₁₀)heteroaryl, each of which is unsubstituted or substituted with one or more R⁷ groups.

In another embodiment, R⁶ is -phenyl.

10 In another embodiment, R¹¹ is -hydrogen, -halo, -CH₃, -NO₂, -CN, -OH, -OCH₃, -NH₂, -C(halo)₃, -CH(halo)₂, or -CH₂(halo).

In another embodiment, R¹¹ is -halo.

In another embodiment, R¹¹ is -Cl.

In another embodiment, R¹¹ is -Br.

In another embodiment, R¹¹ is -F.

15 In another embodiment, R¹¹ is -I.

In another embodiment, R¹¹ is -CH₃.

In another embodiment, q is 1 and R¹² is -halo, -CN, -OH, -NO₂, or -NH₂.

20 In another embodiment, q is 1 and R¹² is -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(C₃-C₇)heterocycle, or -(C₇-C₁₀)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R⁵ groups.

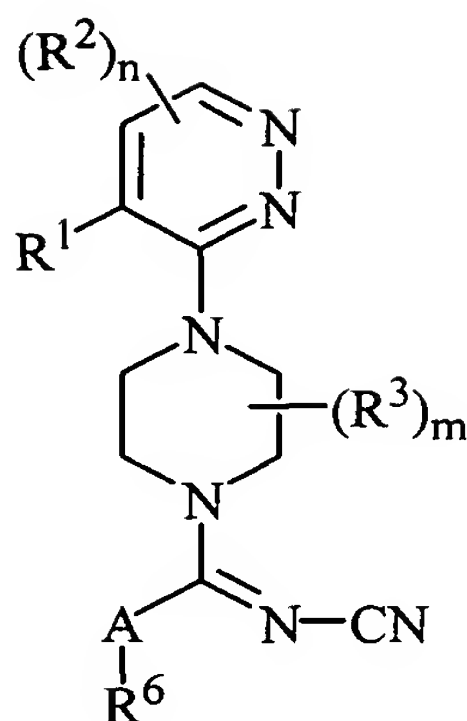
In another embodiment, q is 1 and R¹² is -phenyl, -naphthyl, -(C₁₄)aryl, or -(C₅-C₁₀)heteroaryl, each of which is unsubstituted or substituted with one or more R⁷ groups.

25

4.11 CYANOIMINOPIPERAZINE COMPOUNDS OF FORMULA (IV)

The present invention also encompasses compounds of formula (IV):

30



(IV)

10 and pharmaceutically acceptable salts thereof, where A, R¹, R², R³, R⁶, n, and m are defined above for the Cyanoiminopiperazine Compounds of formula (IV).

In one embodiment, n is 0.

In another embodiment, n is 1.

In another embodiment, n is 2.

15 In one embodiment, m is 0.

In another embodiment, m is 1.

In another embodiment, m is 2.

In another embodiment, A is -NH-.

In another embodiment, A is -N((C₁-C₆)alkyl)-.

20 In another embodiment, A is -N(O(C₁-C₆)alkyl)-.

In another embodiment, A is -O-.

In another embodiment, A is -S-.

In another embodiment, R¹ is -halo.

In another embodiment, R¹ is -Cl.

25 In another embodiment, R¹ is -Br.

In another embodiment, R¹ is -I.

In another embodiment, R¹ is -F.

In another embodiment, R¹ is -CH₃.

In another embodiment, n is one and R² is -halo, -CN, -OH, -NO₂, or -NH₂;

30 In another embodiment, n is 1 and R² is -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-

C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(C₃-C₇)heterocycle, or - (C₇-C₁₀)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R⁵ groups.

In another embodiment, n is 1 and R² is -phenyl, -naphthyl, -(C₁₄)aryl, or -(C₅-
5 C₁₀)heteroaryl, each of which is unsubstituted or substituted with one or more R⁷ groups;

In another embodiment, m is 1 and R³ is -halo, -CN, -OH, -NO₂, or -NH₂.

In another embodiment, m is 1 and R³ is -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-
C₁₀)alkynyl, -(C₃-C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-
C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(C₃-C₇)heterocycle, or -
10 (C₇-C₁₀)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R⁵ groups.

In another embodiment, m is 1 and R³ is -phenyl, -naphthyl, -(C₁₄)aryl or -(C₅-
C₁₀)heteroaryl, each of which is unsubstituted or substituted with one or more R⁷ groups.

In another embodiment, m is 1 and R³ is -CH₃.

15 In another embodiment, m is 1, R³ is -CH₃, and the carbon atom to which the -
R³ is attached is in the (R)-configuration.

In another embodiment, m is 1, R³ is -CH₃, and the carbon atom to which the -
R³ is attached is in the (S)-configuration.

In another embodiment, R⁶ is -phenyl, -naphthyl, -(C₃-C₈)cycloalkyl, -(C₁₄)aryl,
20 or -(C₅-C₁₀)heteroaryl, each of which is unsubstituted or substituted with one or more R⁷ groups.

In another embodiment, R⁶ is -phenyl.

In one embodiment, n and m are 0 and R⁶ is -phenyl. In another embodiment,
n is 0, m is 1, R³ is methyl, and R⁶ is phenyl. In another embodiment, the -phenyl is
25 substituted with a -(C₁-C₆) alkyl group. In another embodiment, the -(C₁-C₆) alkyl group is
substituted at the 4-position of the -phenyl. In another embodiment, the -(C₁-C₆) alkyl group
is a *t*-butyl group substituted at 4-position of the -phenyl. In another embodiment, the -(C₁-
C₆) alkyl group is an *iso*-propyl group substituted at the 4-position of the -phenyl.

In another embodiment, R¹ is -CF₃ or -CHF₂.

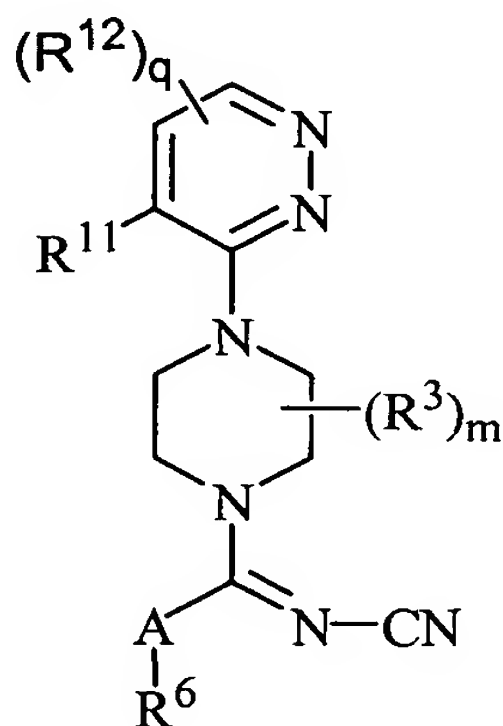
30 In another embodiment, n and m are 0 and R⁶ is -phenyl substituted at its 4-
position with a -CF₃ group.

In another embodiment, n and m are 0, R¹ is -halo or methyl; and R⁶ is -phenyl. In one embodiment, -halo is -Cl. In another embodiment, the -phenyl is substituted with a -(C₁-C₆) alkyl group. In another embodiment, the -(C₁-C₆) alkyl group is substituted at the 4-position of the -phenyl. In another embodiment, the -(C₁-C₆) alkyl group is a *t*-butyl group or an *iso*-propyl group substituted at the 4-position of the -phenyl.

In another embodiment, n and m are 0, R¹ is -halo or methyl; and R⁶ is -phenyl substituted with -CF₃. In another embodiment, -halo is -Cl. In another embodiment, the -CF₃ is substituted at the 4-position of the -phenyl. In another embodiment, -halo is -Cl and the -CF₃ is substituted at the 4-position of the -phenyl.

4.12 CYANOIMINOPIPERAZINE COMPOUNDS OF FORMULA (IVa)

The present invention also encompasses compounds having the formula (IVa):



(IVa)

and pharmaceutically acceptable salts thereof, wherein A, R³, R⁶, R¹¹, R¹², m and q are defined above for the Cyanoiminopiperazine Compounds of formula (IVa).

In one embodiment, q is 0.

In another embodiment, q is 1.

In another embodiment, q is 2.

In one embodiment, m is 0.

In another embodiment, m is 1.

In another embodiment, m is 2.

In another embodiment, A is -NH-.

In another embodiment, A is -N((C₁-C₆)alkyl)-.

In another embodiment, A is -N(O(C₁-C₆)alkyl)-.

In another embodiment, A is -O-.

In another embodiment, A is -S-.

5 In another embodiment, m is 1 and R³ is -halo, -CN, -OH, -NO₂, or -NH₂.

In another embodiment, m is 1 and R³ is -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(C₃-C₇)heterocycle, or -(C₇-C₁₀)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R⁵
10 groups.

In another embodiment, m is 1 and R³ is -phenyl, -naphthyl, -(C₁₄)aryl or -(C₅-C₁₀)heteroaryl, each of which is unsubstituted or substituted with one or more R⁷ groups.

In another embodiment, m is 1 and R³ is -CH₃.

In another embodiment, m is 1, R³ is -CH₃, and the carbon atom to which the -
15 R³ is attached is in the (R)-configuration.

In another embodiment, m is 1, R³ is -CH₃, and the carbon atom to which the -
R³ is attached is in the (S)-configuration.

In another embodiment, R⁶ is -phenyl, -naphthyl, -(C₃-C₈)cycloalkyl, -(C₁₄)aryl, or -(C₅-C₁₀)heteroaryl, each of which is unsubstituted or substituted with one or more R⁷
20 groups.

In another embodiment, R⁶ is -phenyl.

In another embodiment, R¹¹ is -hydrogen, -halo, -CH₃, -NO₂, -CN, -OH, -OCH₃, -NH₂, -C(halo)₃, -CH(halo)₂, or -CH₂(halo).

In another embodiment, R¹¹ is -halo.

25 In another embodiment, R¹¹ is -Cl.

In another embodiment, R¹¹ is -Br.

In another embodiment, R¹¹ is -F.

In another embodiment, R¹¹ is -I.

In another embodiment, R¹¹ is -CH₃.

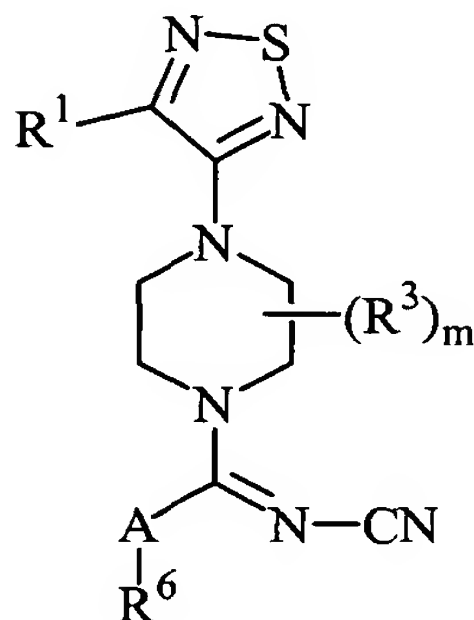
30 In another embodiment, R¹² is -halo, -CN, -OH, -NO₂, or -NH₂.

In another embodiment, R¹² is -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(C₃-C₇)heterocycle, or -(C₇-C₁₀)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R⁵ groups.

In another embodiment, R¹² is -phenyl, -naphthyl, -(C₁₄)aryl, or -(C₅-C₁₀)heteroaryl, each of which is unsubstituted or substituted with one or more R⁷ groups.

4.13 CYANOIMINOPIPERAZINE COMPOUNDS OF FORMULA (V)

The present invention also encompasses compounds of formula (V)



(V)

and pharmaceutically acceptable salts thereof, wherein A, R¹, R³, R⁶, and m are defined above for the Cyanoiminopiperazine Compounds of formula (V).

In one embodiment, m is 0.

In another embodiment, m is 1.

In another embodiment, m is 2.

In another embodiment, A is -NH-

In another embodiment, A is -N((C₁-C₆)alkyl)-.

In another embodiment, A is -N(O(C₁-C₆)alkyl)-.

In another embodiment, A is -O-.

In another embodiment, A is -S-.

In another embodiment, R¹ is -hydrogen.

In another embodiment, R¹ is -halo, -CH₃, -NO₂, -CN, -OH, -OCH₃, -NH₂, -C(halo)₃, -CH(halo)₂, or -CH₂(halo).

In another embodiment, R¹ is -halo.

In another embodiment, R¹ is -Cl.

5 In another embodiment, R¹ is -Br.

In another embodiment, R¹ is -I.

In another embodiment, R¹ is -F.

In another embodiment, R¹ is -CH₃.

In another embodiment, m is 1 and R³ is -halo, -CN, -OH, -NO₂, or -NH₂.

10 In another embodiment, m is 1 and R³ is -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(C₃-C₇)heterocycle, or -(C₇-C₁₀)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R⁵ groups.

15 In another embodiment, m is 1 and R³ is -phenyl, -naphthyl, -(C₁₄)aryl or -(C₅-C₁₀)heteroaryl, each of which is unsubstituted or substituted with one or more R⁷ groups.

In another embodiment, m is 1 and R³ is -CH₃.

In another embodiment, m is 1, R³ is -CH₃, and the carbon atom to which the -R³ is attached is in the (R)-configuration.

20 In another embodiment, m is 1, R³ is -CH₃, and the carbon atom to which the -R³ is attached is in the (S)-configuration.

In another embodiment, R⁶ is -phenyl, -naphthyl, -(C₃-C₈)cycloalkyl, -(C₁₄)aryl, or -(C₅-C₁₀)heteroaryl, each of which is unsubstituted or substituted with one or more R⁷ groups.

25 In another embodiment, R⁶ is -phenyl.

In one embodiment, m is 0 and R⁶ is -phenyl. In another embodiment, m is 1, R³ is methyl, and R⁶ is phenyl. In another embodiment, the -phenyl is substituted with a -(C₁-C₆) alkyl group. In another embodiment, the -(C₁-C₆) alkyl group is substituted at the 4-position of the -phenyl. In another embodiment, the -(C₁-C₆) alkyl group is a *t*-butyl group substituted at 4-position of the -phenyl. In another embodiment, the -(C₁-C₆) alkyl group is an *iso*-propyl group substituted at the 4-position of the -phenyl.

30

In another embodiment, R^1 is $-CF_3$ or $-CHF_2$.

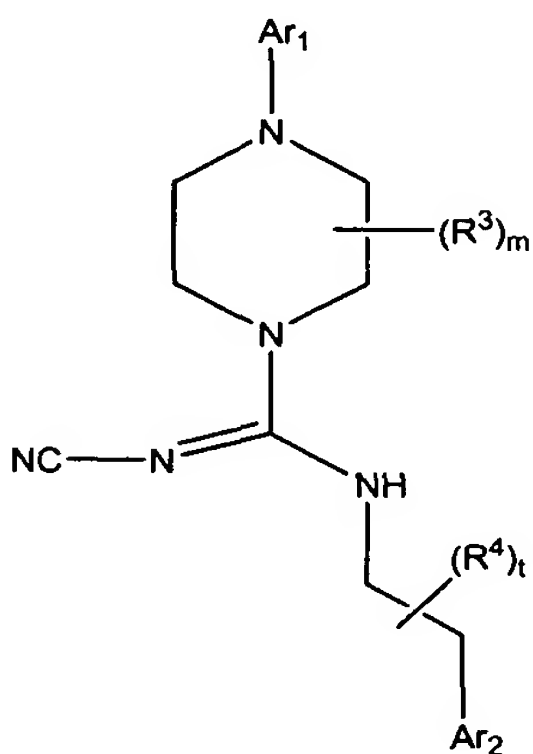
In another embodiment, m is 0 and R^6 is $-phenyl$ substituted at its 4-position with a $-CF_3$ group.

In another embodiment, m is 0, R^1 is $-halo$ or methyl; and R^6 is $-phenyl$. In one embodiment, $-halo$ is $-Cl$. In another embodiment, the $-phenyl$ is substituted with a $-(C_1-C_6)$ alkyl group. In another embodiment, the $-(C_1-C_6)$ alkyl group is substituted at the 4-position of the $-phenyl$. In another embodiment, the $-(C_1-C_6)$ alkyl group is a *t*-butyl group or an *iso*-propyl group substituted at the 4-position of the $-phenyl$.

In another embodiment, m is 0, R^1 is $-halo$ or methyl; and R^6 is $-phenyl$ substituted with $-CF_3$. In another embodiment, $-halo$ is $-Cl$. In another embodiment, the $-CF_3$ is substituted at the 4-position of the $-phenyl$. In another embodiment, $-halo$ is $-Cl$ and the $-CF_3$ is substituted at the 4-position of the $-phenyl$.

4.14 CYANOIMINOPIPERAZINE COMPOUNDS OF FORMULA (VI)

The present invention also encompasses compounds of formula (VI):



(VI)

and pharmaceutically acceptable salts thereof, wherein Ar_1 , Ar_2 , R^3 , R^4 , m , and t are defined above for the Cyanoiminopiperazine Compound of formula (VI).

In one embodiment Ar_1 is a pyridyl group.

In another embodiment, Ar_1 is a pyrimidinyl group.

In another embodiment, Ar_1 is a pyridazinyl group.

In another embodiment, Ar_1 is a pyrazinyl group.

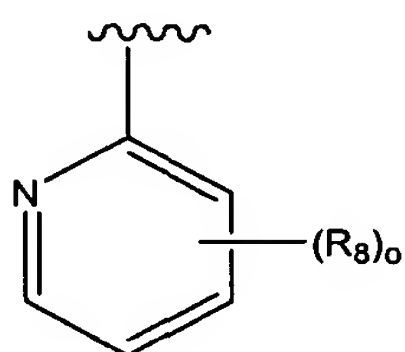
In another embodiment, Ar₁ is a thiadiazolyl group.

In another embodiment, Ar₂ is a benzothiazolyl group.

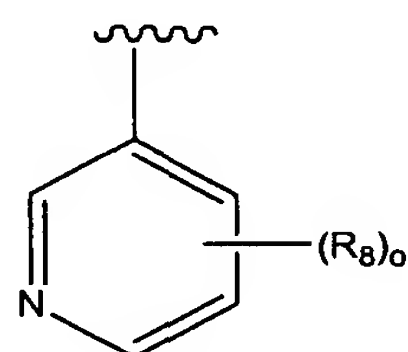
In another embodiment, Ar₂ is a benzoimidazolyl group.

In another embodiment, Ar₂ is a benzooxazolyl group.

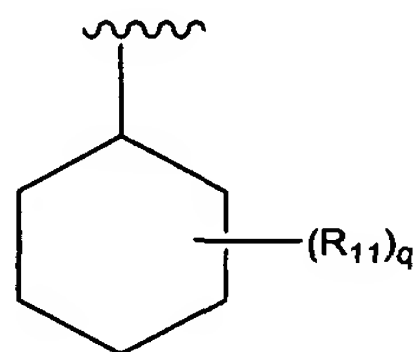
In another embodiment, Ar₂ is



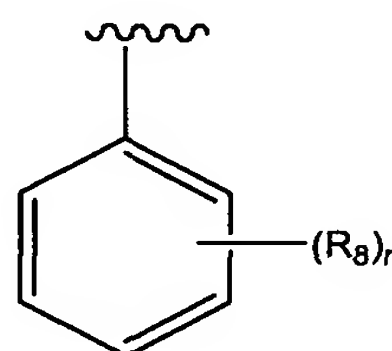
In another embodiment, Ar₂ is



In another embodiment, Ar₂ is

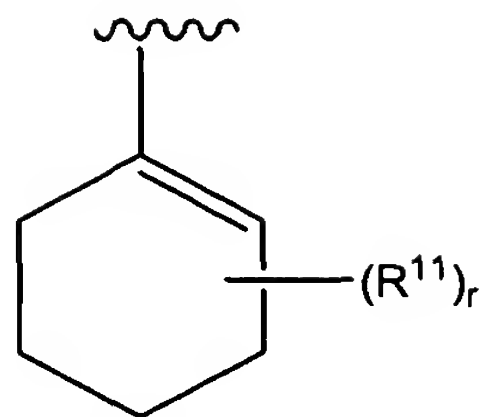


In another embodiment, Ar₂ is



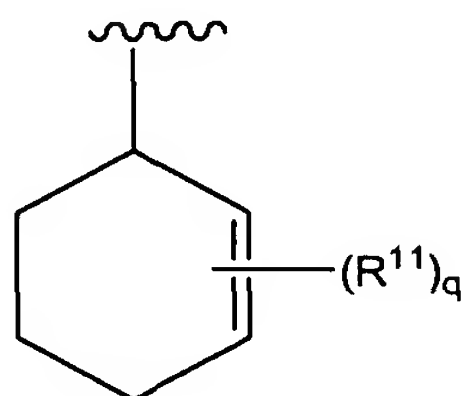
In another embodiment, Ar₂ is

5 .



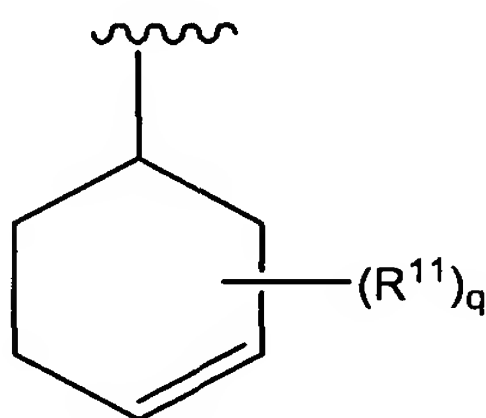
In another embodiment, Ar_2 is

10



In another embodiment, Ar_2 is

15



In another embodiment, R_1 is -H.

20

In another embodiment, R_1 is -halo.

In another embodiment, R_1 is -Cl.

In another embodiment, R_1 is -Br.

In another embodiment, R_1 is -I.

In another embodiment, R_1 is -F.

25

In another embodiment, R_1 is -CH₃.

In another embodiment, R_1 is -NO₂.

In another embodiment, R_1 is -CN.

In another embodiment, R_1 is -OH.

In another embodiment, R_1 is -OCH₃.

30

In another embodiment, R_1 is -NH₂.

In another embodiment, R_1 is -C(halo)₃.

In another embodiment, R₁ is -CH(halo)₂.

In another embodiment, R₁ is -CH₂(halo).

In another embodiment, R₂ is -halo, -CN, -OH, -NO₂, or -NH₂.

In another embodiment, R₂ is -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R₅ groups; or

In another embodiment, R₂ is -phenyl, -naphthyl, -(C₁₄)aryl or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R₆ groups;

In another embodiment, R₃ is -halo, -CN, -OH, -NO₂, or -NH₂.

In another embodiment, R₃ is -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R₅ groups.

In another embodiment, R₃ is -phenyl, -naphthyl, -(C₁₄)aryl or -(5- to 10-membered) heteroaryl, each of which is unsubstituted or substituted with one or more R₆ groups.

In another embodiment, R₃ is -CH₃.

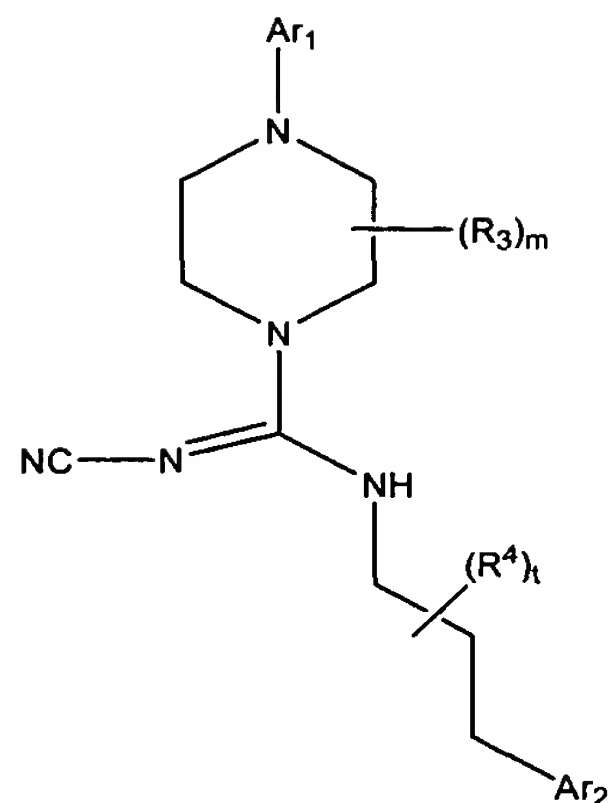
In another embodiment, m is 1, R³ is -CH₃, and the carbon atom to which the -R³ is attached is in the (R)-configuration.

In another embodiment, m is 1, R³ is -CH₃, and the carbon atom to which the -R³ is attached is in the (S)-configuration.

4.15 CYANOIMINOPIPERAZINE COMPOUNDS OF FORMULA (VII)

The present invention also encompasses compounds of formula (VII):

5



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(VII)

and pharmaceutically acceptable salts thereof, wherein Ar_1 , Ar_2 , R_3 , R_4 , m , and t are defined above for formula (VI).

In one embodiment Ar_1 is a pyridyl group.

In another embodiment, Ar_1 is a pyrimidinyl group.

15

In another embodiment, Ar_1 is a pyridazinyl group.

In another embodiment, Ar_1 is a pyrazinyl group.

In another embodiment, Ar_1 is a thiadiazolyl group.

In another embodiment, Ar_2 is a benzothiazolyl group.

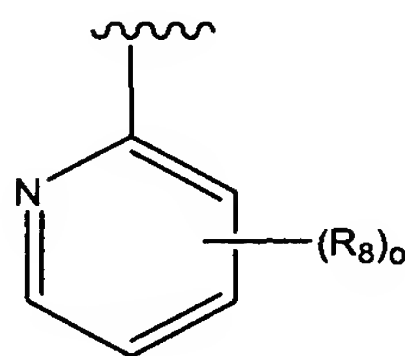
In another embodiment, Ar_2 is a benzoimidazolyl group.

20

In another embodiment, Ar_2 is a benzooxazolyl group.

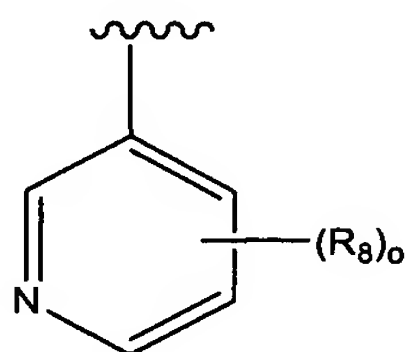
In another embodiment, Ar_2 is

25



In another embodiment, Ar_2 is

30



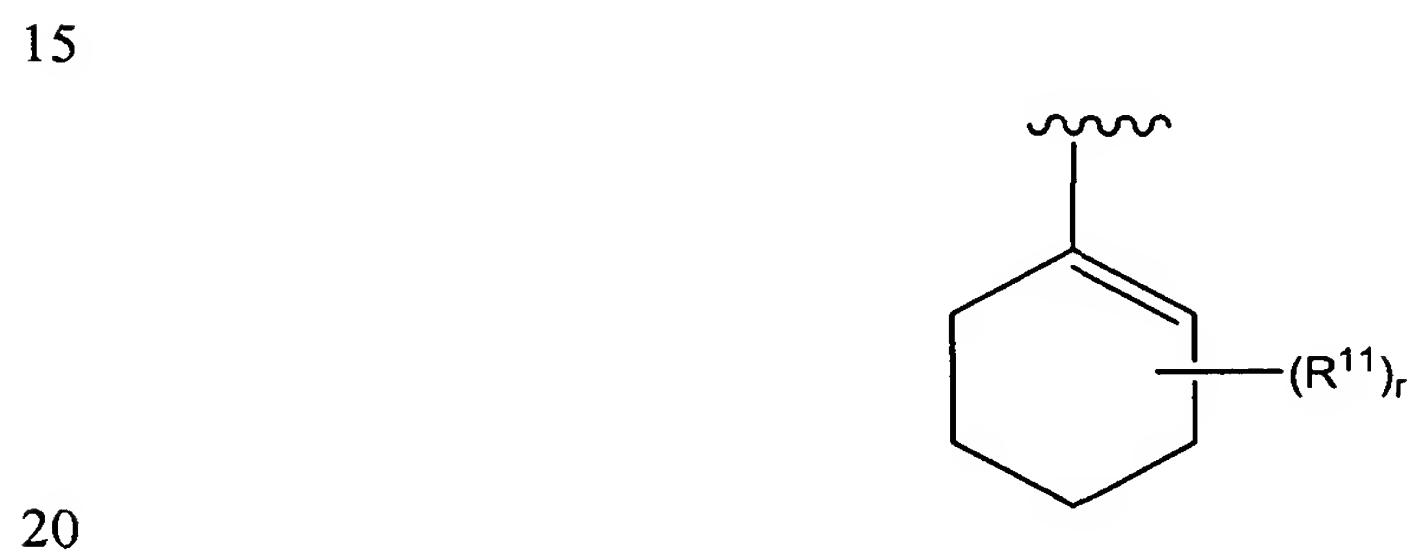
In another embodiment, Ar₂ is



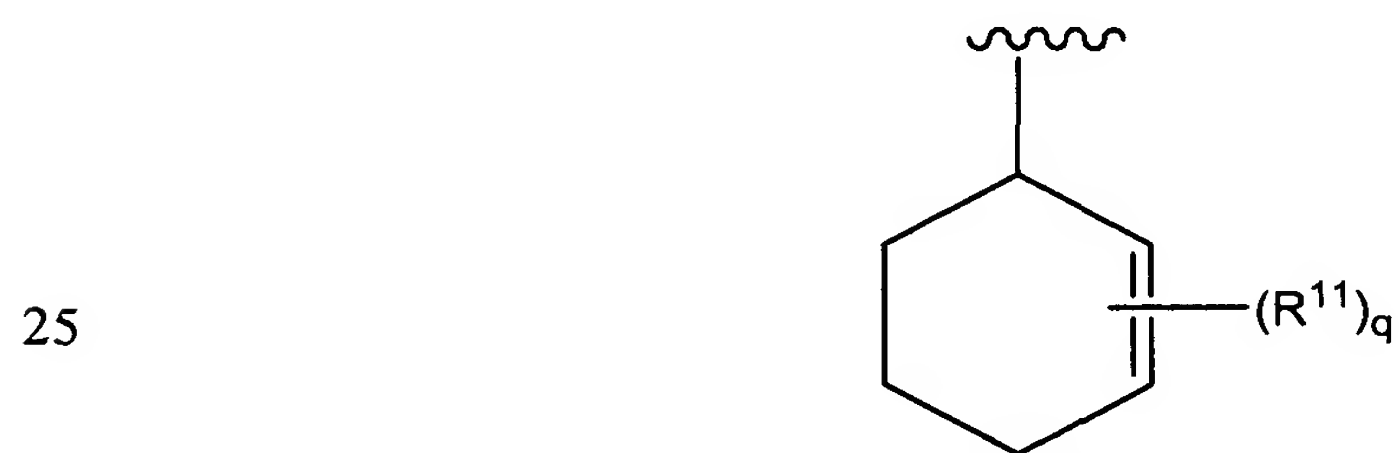
In another embodiment, Ar₂ is



In another embodiment, Ar₂ is



In another embodiment, Ar₂ is



In another embodiment, Ar₂ is



In another embodiment, R₁ is -H.

In another embodiment, R₁ is -halo.

In another embodiment, R₁ is -Cl.

5 In another embodiment, R₁ is -Br.

In another embodiment, R₁ is -I.

In another embodiment, R₁ is -F.

In another embodiment, R₁ is -CH₃.

In another embodiment, R₁ is -NO₂.

10 In another embodiment, R₁ is -CN.

In another embodiment, R₁ is -OH.

In another embodiment, R₁ is -OCH₃.

In another embodiment, R₁ is -NH₂.

In another embodiment, R₁ is -C(halo)₃.

15 In another embodiment, R₁ is -CH(halo)₂.

In another embodiment, R₁ is -CH₂(halo).

In another embodiment, R₂ is -halo, -CN, -OH, -NO₂, or -NH₂.

In another embodiment, R₂ is -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R₅ groups; or

25 In another embodiment, R₂ is -phenyl, -naphthyl, -(C₁₄)aryl or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R₆ groups;

In another embodiment, R₃ is -halo, -CN, -OH, -NO₂, or -NH₂.

In another embodiment, R₃ is -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R₅ groups.

In another embodiment, R_3 is -phenyl, -naphthyl, $-(C_{14})$ aryl or -(5- to 10-membered) heteroaryl, each of which is unsubstituted or substituted with one or more R_6 groups.

In another embodiment, R_3 is $-CH_3$.

5 In another embodiment, m is 1, R^3 is $-CH_3$, and the carbon atom to which the R^3 is attached is in the (R)-configuration.

In another embodiment, m is 1, R^3 is $-CH_3$, and the carbon atom to which the R^3 is attached is in the (S)-configuration.

10 **4.16 CYANOIMINOPIPERAZINE COMPOUNDS OF FORMULA (I), (IA), (IB), (II), (IIA), (III), (IIIA), (IIIB), (IIIC), (IV), (IVA), (V), (VI), AND (VII)**

Certain Cyanoiminopiperazine Compounds may have asymmetric centers and therefore exist in different enantiomeric and diastereomeric forms. This invention relates to the use of all optical isomers and stereoisomers of the Cyanoiminopiperazine Compounds, and
15 mixtures thereof, and to all pharmaceutical compositions and methods of treatment that may employ or contain them.

In the Cyanoiminopiperazine Compounds each R^3 can be on any carbon of the piperazine ring. In one embodiment, the Cyanoiminopiperazine Compounds have only one R^3 group, and that R^3 group is attached to a carbon atom adjacent to the nitrogen atom
20 attached to the pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, or thiadiazolyl group. In another embodiment, the Cyanoiminopiperazine Compound has only one R^3 group, and that R^3 group is attached to a carbon atom adjacent to the nitrogen atom attached to the $-C(=N-CN)-A-R^6$ group, $-C(=N-CN)-NH$ -phenethyl group, $-C(=N-CN)-NH$ -phenpropyl group, or $-C(=N-CN)-NH-(R^9)$ -phenyl.

25 In another embodiment, two R^3 groups are on a single atom of the piperazine ring. In another embodiment, an R^3 group is attached to a carbon atom adjacent to the nitrogen atom attached to the pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, or thiadiazolyl group and another R^3 group is attached to a carbon atom adjacent to the nitrogen atom attached to the $-C(=N-CN)-A-R^6$ group, $-C(=N-CN)-NH$ -phenethyl group, $-C(=N-CN)-NH$ -
30 phenpropyl group, or $-C(=N-CN)-NH-(R^9)$ -phenyl.

In another embodiment, the Cyanoiminopiperazine Compound has two R^3 groups, each being attached to a different carbon atom adjacent to a nitrogen atom attached to

the pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, or thiadiazolyl group. In another embodiment, the Cyanoiminopiperazine Compound has two R^3 groups, each being attached to a different carbon atom adjacent to a nitrogen atom attached to the $-C(=N-CN)-A-R^6$ group, $-C(=N-CN)-NH$ -phenethyl group, $-C(=N-CN)-NH$ -phenpropyl group, or $-C(=N-CN)-$
5 $NH-(R^9)$ -phenyl.

In one embodiment, wherein the Cyanoiminopiperazine Compound has one or two R^3 groups, the carbon atom to which an R^3 group is attached has the (R) configuration. In another embodiment, wherein the Cyanoiminopiperazine Compound has one or two R^3 groups, the carbon atom to which the R^3 group is attached has the (S) configuration. In
10 another embodiment, the Cyanoiminopiperazine Compound has one or two R^3 groups, and at least one of the carbon atoms to which an R^3 group is attached has the (R) configuration. In another embodiment, the Cyanoiminopiperazine Compound has one or two R^3 groups, and at least one of the carbon atoms to which an R^3 group is attached has the (S) configuration.

In another embodiment, the Cyanoiminopiperazine Compound has one or two
15 R^3 groups, an R^3 group is attached to a carbon atom adjacent to a nitrogen atom attached to the pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, or thiadiazolyl group, and the carbon to which the R^3 group is attached is in the (R) configuration. In another embodiment, the Cyanoiminopiperazine Compound has one or two R^3 groups, an R^3 group is attached to a carbon atom adjacent to a nitrogen attached to the pyridyl, pyrimidinyl, pyrazinyl,
20 pyridazinyl, or thiadiazolyl group, the carbon to which the R^3 group is attached is in the (R) configuration, and R^3 is $-(C_1-C_4)$ alkyl unsubstituted or substituted with one or more halo groups. In another embodiment, the Cyanoiminopiperazine Compound has one or two R^3 groups, an R^3 group is attached to a carbon atom adjacent to a nitrogen attached to the pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, or thiadiazolyl group, the carbon to which the R^3
25 group is attached is in the (R) configuration, and R^3 is $-CH_3$. In another embodiment, the Cyanoiminopiperazine Compound has one or two R^3 groups, an R^3 group is attached to a carbon atom adjacent to a nitrogen attached to the pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, or thiadiazolyl group, the carbon to which the R^3 group is attached is in the (R) configuration, and R^3 is $-CF_3$. In another embodiment, the Cyanoiminopiperazine Compound
30 has one or two R^3 groups, an R^3 group is attached to a carbon atom adjacent to a nitrogen

attached to the pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, or thiadiazolyl group, the carbon to which the R^3 group is attached is in the (R) configuration, and R^3 is $-CH_2CH_3$.

In another embodiment, the Cyanoiminopiperazine Compound has one or two R^3 groups, an R^3 group is attached to a carbon atom adjacent to a nitrogen atom attached to the $-C(=N-CN)-A-R^6$ group, $-C(=N-CN)-NH$ -phenethyl group, $-C(=N-CN)-NH$ -phenpropyl group, or $-C(=N-CN)-NH-(R^9)$ -phenyl, and the carbon to which the R^3 group is attached is in the (R) configuration. In another embodiment, the Cyanoiminopiperazine Compound has one or two R^3 groups, an R^3 group is attached to a carbon atom adjacent to a nitrogen attached to the $-C(=N-CN)-A-R^6$ group, $-C(=N-CN)-NH$ -phenethyl group, $-C(=N-CN)-NH$ -phenpropyl group, or $-C(=N-CN)-NH-(R^9)$ -phenyl, the carbon to which the R^3 group is attached is in the (R) configuration, and R^3 is $-(C_1-C_4)$ alkyl unsubstituted or substituted with one or more halo groups. In another embodiment, the Cyanoiminopiperazine Compound has one or two R^3 groups, an R^3 group is attached to a carbon atom adjacent to a nitrogen attached to the $-C(=N-CN)-A-R^6$ group, $-C(=N-CN)-NH$ -phenethyl group, $-C(=N-CN)-NH$ -phenpropyl group, or $-C(=N-CN)-NH-(R^9)$ -phenyl, the carbon to which the R^3 group is attached is in the (R) configuration, and R^3 is $-CH_3$. In another embodiment, the Cyanoiminopiperazine Compound has one or two R^3 groups, an R^3 group is attached to a carbon atom adjacent to a nitrogen attached to the $-C(=N-CN)-A-R^6$ group, $-C(=N-CN)-NH$ -phenethyl group, $-C(=N-CN)-NH$ -phenpropyl group, or $-C(=N-CN)-NH-(R^9)$ -phenyl, the carbon to which the R^3 group is attached is in the (R) configuration, and R^3 is $-CF_3$. In another embodiment, the Cyanoiminopiperazine Compound has one or two R^3 groups, an R^3 group is attached to a carbon atom adjacent to a nitrogen attached to the $-C(=N-CN)-A-R^6$ group, $-C(=N-CN)-NH$ -phenethyl group, $-C(=N-CN)-NH$ -phenpropyl group, or $-C(=N-CN)-NH-(R^9)$ -phenyl, the carbon to which the R^3 group is attached is in the (R) configuration, and R^3 is $-CH_2CH_3$.

In another embodiment, the Cyanoiminopiperazine Compound has one or two R^3 groups, an R^3 group is attached to a carbon atom adjacent to a nitrogen atom attached to the pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, or thiadiazolyl group, and the carbon to which the R^3 group is attached is in the (S) configuration. In another embodiment, the Cyanoiminopiperazine Compound has one or two R^3 groups, an R^3 group is attached to a carbon atom adjacent to a nitrogen attached to the pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, or thiadiazolyl group, the carbon to which the R^3 group is attached is in the (S)

configuration, and R^3 is $-(C_1-C_4)$ alkyl unsubstituted or substituted with one or more halo groups. In another embodiment, the Cyanoiminopiperazine Compound has one or two R^3 groups, an R^3 group is attached to a carbon atom adjacent to a nitrogen attached to the pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, or thiadiazolyl group, the carbon to which the R^3 group is attached is in the (S) configuration, and R^3 is $-CH_3$. In another embodiment, the Cyanoiminopiperazine Compound has one or two R^3 groups, an R^3 group is attached to a carbon atom adjacent to a nitrogen attached to the pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, or thiadiazolyl group, the carbon to which the R^3 group is attached is in the (S) configuration, and R^3 is $-CF_3$. In another embodiment, the Cyanoiminopiperazine Compound has one or two R^3 groups, an R^3 group is attached to a carbon atom adjacent to a nitrogen attached to the pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, or thiadiazolyl group, the carbon to which the R^3 group is attached is in the (S) configuration, and R^3 is $-CH_2CH_3$.

In another embodiment, the Cyanoiminopiperazine Compound has one or two R^3 groups, an R^3 group is attached to a carbon atom adjacent to a nitrogen atom attached to the $-C(=N-CN)-A-R^6$ group, $-C(=N-CN)-NH$ -phenethyl group, $-C(=N-CN)-NH$ -phenpropyl group, or $-C(=N-CN)-NH-(R^9)$ -phenyl, and the carbon to which the R^3 group is attached is in the (S) configuration. In another embodiment, the Cyanoiminopiperazine Compound has one or two R^3 groups, an R^3 group is attached to a carbon atom adjacent to a nitrogen attached to the $-C(=N-CN)-A-R^6$ group, $-C(=N-CN)-NH$ -phenethyl group, $-C(=N-CN)-NH$ -phenpropyl group, or $-C(=N-CN)-NH-(R^9)$ -phenyl, the carbon to which the R^3 group is attached is in the (S) configuration, and R^3 is $-(C_1-C_4)$ alkyl unsubstituted or substituted with one or more halo groups. In another embodiment, the Cyanoiminopiperazine Compound has one or two R^3 groups, an R^3 group is attached to a carbon atom adjacent to a nitrogen attached to the $-C(=N-CN)-A-R^6$ group, $-C(=N-CN)-NH$ -phenethyl group, $-C(=N-CN)-NH$ -phenpropyl group, or $-C(=N-CN)-NH-(R^9)$ -phenyl, the carbon to which the R^3 group is attached is in the (S) configuration, and R^3 is $-CH_3$. In another embodiment, the Cyanoiminopiperazine Compound has one or two R^3 groups, an R^3 group is attached to a carbon atom adjacent to a nitrogen attached to the $-C(=N-CN)-A-R^6$ group, $-C(=N-CN)-NH$ -phenethyl group, $-C(=N-CN)-NH$ -phenpropyl group, or $-C(=N-CN)-NH-(R^9)$ -phenyl, the carbon to which the R^3 group is attached is in the (S) configuration, and R^3 is $-CF_3$. In another embodiment, the Cyanoiminopiperazine Compound has one or two R^3 groups, an R^3 group is attached to a

carbon atom adjacent to a nitrogen attached to the $-C(=N-CN)-A-R^6$ group, $-C(=N-CN)-NH$ -phenethyl group, $-C(=N-CN)-NH$ -phenpropyl group, or $-C(=N-CN)-NH-(R^9)$ -phenyl, the carbon to which the R^3 group is attached is in the (S) configuration, and R^3 is $-CH_2CH_3$.

In another embodiment, the Cyanoiminopiperazine Compound has only one R^3 group, the R^3 group is attached to a carbon atom adjacent to a nitrogen atom attached to the pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, or thiadiazolyl group, and the carbon to which the R^3 group is attached is in the (R) configuration. In another embodiment, the Cyanoiminopiperazine Compound has only one R^3 group, the R^3 group is attached to a carbon atom adjacent to a nitrogen attached to the pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, or thiadiazolyl group, the carbon to which the R^3 group is attached is in the (R) configuration, and R^3 is $-(C_1-C_4)$ alkyl unsubstituted or substituted with one or more halo groups. In another embodiment, the Cyanoiminopiperazine Compound has only one R^3 group, the R^3 group is attached to a carbon atom adjacent to a nitrogen attached to the pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, or thiadiazolyl group, the carbon to which the R^3 group is attached is in the (R) configuration, and R^3 is $-CH_3$. In another embodiment, the Cyanoiminopiperazine Compound has only one R^3 group, the R^3 group is attached to a carbon atom adjacent to a nitrogen attached to the pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, or thiadiazolyl group, the carbon to which the R^3 group is attached is in the (R) configuration, and R^3 is $-CF_3$. In another embodiment, the Cyanoiminopiperazine Compound has only one R^3 group, the R^3 group is attached to a carbon atom adjacent to a nitrogen attached to the pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, or thiadiazolyl group, the carbon to which the R^3 group is attached is in the (R) configuration, and R^3 is $-CH_2CH_3$.

In another embodiment, the Cyanoiminopiperazine Compound has only one R^3 group, the R^3 group is attached to a carbon atom adjacent to a nitrogen atom attached to the $-C(=N-CN)-A-R^6$ group, $-C(=N-CN)-NH$ -phenethyl group, $-C(=N-CN)-NH$ -phenpropyl group, or $-C(=N-CN)-NH-(R^9)$ -phenyl, and the carbon to which the R^3 group is attached is in the (R) configuration. In another embodiment, the Cyanoiminopiperazine Compound has only one R^3 group, the R^3 group is attached to a carbon atom adjacent to a nitrogen attached to the $-C(=N-CN)-A-R^6$ group, $-C(=N-CN)-NH$ -phenethyl group, $-C(=N-CN)-NH$ -phenpropyl group, or $-C(=N-CN)-NH-(R^9)$ -phenyl, the carbon to which the R^3 group is attached is in the (R) configuration, and R^3 is $-(C_1-C_4)$ alkyl unsubstituted or substituted with one or more halo

pyrazinyl, pyridazinyl, or thiadiazolyl group, the carbon to which the R³ group is attached is in the (S) configuration, and R³ is -CH₂CH₃.

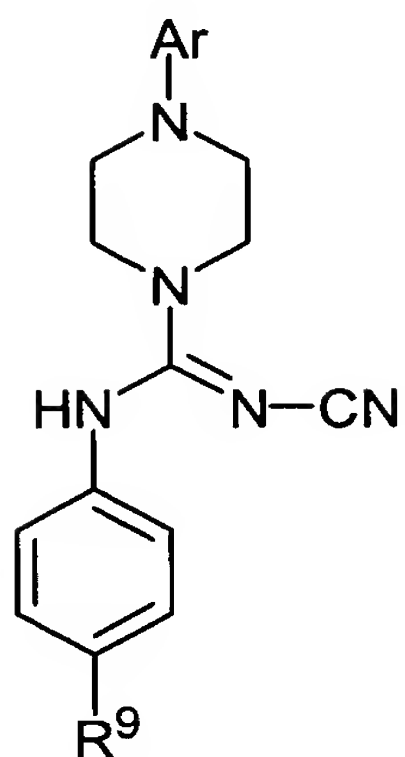
In another embodiment, the Cyanoiminopiperazine Compound has only one R³ group, the R³ group is attached to a carbon atom adjacent to a nitrogen atom attached to the -
5 C(=N-CN)-A-R⁶ group, -C(=N-CN)-NH-phenethyl group, -C(=N-CN)-NH-phenpropyl group, or -C(=N-CN)-NH-(R⁹)-phenyl, and the carbon to which the R³ group is attached is in the (S) configuration. In another embodiment, the Cyanoiminopiperazine Compound has only one R³ group, the R³ group is attached to a carbon atom adjacent to a nitrogen attached to the -
C(=N-CN)-A-R⁶ group, -C(=N-CN)-NH-phenethyl group, -C(=N-CN)-NH-phenpropyl group,
10 or -C(=N-CN)-NH-(R⁹)-phenyl, the carbon to which the R³ group is attached is in the (S) configuration, and R³ is -(C₁-C₄)alkyl unsubstituted or substituted with one or more halo groups. In another embodiment, the Cyanoiminopiperazine Compound has only one R³ group, the R³ group is attached to a carbon atom adjacent to a nitrogen attached to the -C(=N-CN)-A-R⁶ group, -C(=N-CN)-NH-phenethyl group, -C(=N-CN)-NH-phenpropyl group, or -
15 C(=N-CN)-NH-(R⁹)-phenyl, the carbon to which the R³ group is attached is in the (S) configuration, and R³ is -CH₃. In another embodiment, the Cyanoiminopiperazine Compound has only one R³ group, the R³ group is attached to a carbon atom adjacent to a nitrogen attached to the -C(=N-CN)-A-R⁶ group, -C(=N-CN)-NH-phenethyl group, -C(=N-CN)-NH-phenpropyl group, or -C(=N-CN)-NH-(R⁹)-phenyl, the carbon to which the R³ group is
20 attached is in the (S) configuration, and R³ is -CF₃. In another embodiment, the Cyanoiminopiperazine Compound has only one R³ group, the R³ group is attached to a carbon atom adjacent to a nitrogen attached to the -C(=N-CN)-A-R⁶ group, -C(=N-CN)-NH-phenethyl group, -C(=N-CN)-NH-phenpropyl group, or -C(=N-CN)-NH-(R⁹)-phenyl, the carbon to which the R³ group is attached is in the (R) configuration, and R³ is -CH₂CH₃.

25 The present invention includes the Cyanoiminopiperazine Compounds, and the pharmaceutically acceptable salts thereof, wherein one or more hydrogen, carbon or other atoms are replaced by isotopes thereof. Such compounds may be useful as research and diagnostic tools in metabolism pharmacokinetic studies and in binding assays.

Illustrative Cyanoiminopiperazine Compounds are listed below in Tables 1-8:

30

Table 1



VI

and pharmaceutically acceptable salts thereof, wherein:

Compound	Ar	R⁹
AAA	-2-(3-chloropyridyl)	-t-butyl
AAB	-2-(3-chloropyridyl)	-iso-butyl
AAC	-2-(3-chloropyridyl)	-sec-butyl
AAD	-2-(3-chloropyridyl)	-cyclohexyl
AAE	-2-(3-chloropyridyl)	-t-butoxy
AAF	-2-(3-chloropyridyl)	-isopropoxy
AAG	-2-(3-chloropyridyl)	-CF ₃
AAH	-2-(3-chloropyridyl)	-CH ₂ CF ₃
AAI	-2-(3-chloropyridyl)	-OCF ₃
AAJ	-2-(3-chloropyridyl)	-Cl
AAK	-2-(3-chloropyridyl)	-Br
AAL	-2-(3-chloropyridyl)	-I
AAM	-2-(3-chloropyridyl)	-n-butyl
AAN	-2-(3-chloropyridyl)	-n-propyl
AAO	-2-(3-fluoropyridyl)	-t-butyl
AAP	-2-(3-fluoropyridyl)	-iso-butyl

5	AAQ	-2-(3-fluoropyridyl)	-sec-butyl
	AAR	-2-(3-fluoropyridyl)	-cyclohexyl
	AAS	-2-(3-fluoropyridyl)	-t-butoxy
	AAT	-2-(3-fluoropyridyl)	-isopropoxy
	AAU	-2-(3-fluoropyridyl)	-CF ₃
10	AAV	-2-(3-fluoropyridyl)	-CH ₂ CF ₃
	AAW	-2-(3-fluoropyridyl)	-OCF ₃
	AAX	-2-(3-fluoropyridyl)	-Cl
	AAZ	-2-(3-fluoropyridyl)	-Br
	ABZ	-2-(3-fluoropyridyl)	-I
15	ABA	-2-(3-fluoropyridyl)	-n-butyl
	ABB	-2-(3-fluoropyridyl)	-n-propyl
	ABC	-2-(3-methylpyridyl)	-t-butyl
	ABD	-2-(3-methylpyridyl)	-iso-butyl
	ABE	-2-(3-methylpyridyl)	-sec-butyl
20	ABF	-2-(3-methylpyridyl)	-cyclohexyl
	ABG	-2-(3-methylpyridyl)	-t-butoxy
	ABH	-2-(3-methylpyridyl)	-isopropoxy
	ABI	-2-(3-methylpyridyl)	-CF ₃
	ABJ	-2-(3-methylpyridyl)	-CH ₂ CF ₃
25	ABK	-2-(3-methylpyridyl)	-OCF ₃
	ABL	-2-(3-methylpyridyl)	-Cl
	ABM	-2-(3-methylpyridyl)	-Br
	ABN	-2-(3-methylpyridyl)	-I
	ABO	-2-(3-methylpyridyl)	-n-butyl
	ABP	-2-(3-methylpyridyl)	-n-propyl
	ABQ	-2-(3-CF ₃ -pyridyl)	-t-butyl
	ABR	-2-(3-CF ₃ -pyridyl)	-iso-butyl
	ABS	-2-(3-CF ₃ -pyridyl)	-sec-butyl

5	ABT	-2-(3-CF ₃ -pyridyl)	-cyclohexyl
	ABU	-2-(3-CF ₃ -pyridyl)	-t-butoxy
	ABV	-2-(3-CF ₃ -pyridyl)	-isopropoxy
	ABW	-2-(3-CF ₃ -pyridyl)	-CF ₃
	ABX	-2-(3-CF ₃ -pyridyl)	-CH ₂ CF ₃
10	ABY	-2-(3-CF ₃ -pyridyl)	-OCF ₃
	ABZ	-2-(3-CF ₃ -pyridyl)	-Cl
	ACA	-2-(3-CF ₃ -pyridyl)	-Br
	ACB	-2-(3-CF ₃ -pyridyl)	-I
	ACC	-2-(3-CF ₃ -pyridyl)	-n-butyl
15	ACD	-2-(3-CF ₃ -pyridyl)	-n-propyl
	ACE	-2-(3-CHF ₂ -pyridyl)	-t-butyl
	ACF	-2-(3-CHF ₂ -pyridyl)	-iso-butyl
	ACG	-2-(3-CHF ₂ -pyridyl)	-sec-butyl
	ACH	-2-(3-CHF ₂ -pyridyl)	-cyclohexyl
20	ACI	-2-(3-CHF ₂ -pyridyl)	-t-butoxy
	ACJ	-2-(3-CHF ₂ -pyridyl)	-isopropoxy
	ACK	-2-(3-CHF ₂ -pyridyl)	-CF ₃
	ACL	-2-(3-CHF ₂ -pyridyl)	-CH ₂ CF ₃
	ACM	-2-(3-CHF ₂ -pyridyl)	-OCF ₃
25	ACN	-2-(3-CHF ₂ -pyridyl)	-Cl
	ACO	-2-(3-CHF ₂ -pyridyl)	-Br
	ACP	-2-(3-CHF ₂ -pyridyl)	-I
	ACQ	-2-(3-CHF ₂ -pyridyl)	-n-butyl
	ACR	-2-(3-CHF ₂ -pyridyl)	-n-propyl
	ACS	-2-(3-hydroxypyridyl)	-t-butyl
	ACT	-2-(3-hydroxypyridyl)	-iso-butyl
	ACU	-2-(3-hydroxypyridyl)	-sec-butyl
	ACV	-2-(3-hydroxypyridyl)	-cyclohexyl

5	ACW	-2-(3-hydroxypyridyl)	-t-butoxy
	ACX	-2-(3-hydroxypyridyl)	-isopropoxy
	ACY	-2-(3-hydroxypyridyl)	-CF ₃
	ACZ	-2-(3-hydroxypyridyl)	-CH ₂ CF ₃
	ADA	-2-(3-hydroxypyridyl)	-OCF ₃
10	ADB	-2-(3-hydroxypyridyl)	-Cl
	ADC	-2-(3-hydroxypyridyl)	-Br
	ADD	-2-(3-hydroxypyridyl)	-I
	ADE	-2-(3-hydroxypyridyl)	-n-butyl
	ADF	-2-(3-hydroxypyridyl)	-n-propyl
15	ADG	-2-(3-nitropyridyl)	-t-butyl
	ADH	-2-(3-nitropyridyl)	-iso-butyl
	ADI	-2-(3-nitropyridyl)	-sec-butyl
	ADJ	-2-(3-nitropyridyl)	-cyclohexyl
	ADK	-2-(3-nitropyridyl)	-t-butoxy
20	ADL	-2-(3-nitropyridyl)	-isopropoxy
	ADM	-2-(3-nitropyridyl)	-CF ₃
	ADN	-2-(3-nitropyridyl)	-CH ₂ CF ₃
	ADO	-2-(3-nitropyridyl)	-OCF ₃
	ADP	-2-(3-nitropyridyl)	-Cl
25	ADQ	-2-(3-nitropyridyl)	-Br
	ADR	-2-(3-nitropyridyl)	-I
	ADS	-2-(3-nitropyridyl)	-n-butyl
	ADT	-2-(3-nitropyridyl)	-n-propyl
	ADU	-2-(3-cyanopyridyl)	-t-butyl
	ADV	-2-(3-cyanopyridyl)	-iso-butyl
	ADW	-2-(3-cyanopyridyl)	-sec-butyl
	ADX	-2-(3-cyanopyridyl)	-cyclohexyl
	ADY	-2-(3-cyanopyridyl)	-t-butoxy

5	ADZ	-2-(3-cyanopyridyl)	-isopropoxy
	AEA	-2-(3-cyanopyridyl)	-CF ₃
	AEB	-2-(3-cyanopyridyl)	-CH ₂ CF ₃
	AEC	-2-(3-cyanopyridyl)	-OCF ₃
	AED	-2-(3-cyanopyridyl)	-Cl
10	AEE	-2-(3-cyanopyridyl)	-Br
	AEF	-2-(3-cyanopyridyl)	-I
	AEG	-2-(3-cyanopyridyl)	-n-butyl
	AEH	-2-(3-cyanopyridyl)	-n-propyl
	AEI	-2-(3-bromopyridyl)	-t-butyl
15	AEJ	-2-(3-bromopyridyl)	-iso-butyl
	AEK	-2-(3-bromopyridyl)	-sec-butyl
	AEL	-2-(3-bromopyridyl)	-cyclohexyl
	AEM	-2-(3-bromopyridyl)	-t-butoxy
	AEN	-2-(3-bromopyridyl)	-isopropoxy
20	AEO	-2-(3-bromopyridyl)	-CF ₃
	AEP	-2-(3-bromopyridyl)	-CH ₂ CF ₃
	AEQ	-2-(3-bromopyridyl)	-OCF ₃
	AER	-2-(3-bromopyridyl)	-Cl
	AES	-2-(3-bromopyridyl)	-Br
25	AET	-2-(3-bromopyridyl)	-I
	AEU	-2-(3-bromopyridyl)	-n-butyl
	AEV	-2-(3-bromopyridyl)	-n-propyl
	AEW	-2-(3-iodopyridyl)	-t-butyl
	AEX	-2-(3-iodopyridyl)	-iso-butyl
	AEY	-2-(3-iodopyridyl)	-sec-butyl
	AEZ	-2-(3-iodopyridyl)	-cyclohexyl
	AFA	-2-(3-iodopyridyl)	-t-butoxy
	AFB	-2-(3-iodopyridyl)	-isopropoxy

5	AFC	-2-(3-iodopyridyl)	-CF ₃
	AFD	-2-(3-iodopyridyl)	-CH ₂ CF ₃
	AFE	-2-(3-iodopyridyl)	-OCF ₃
	AFF	-2-(3-iodopyridyl)	-Cl
	AFG	-2-(3-iodopyridyl)	-Br
10	AFH	-2-(3-iodopyridyl)	-I
	AFI	-2-(3-iodopyridyl)	-n-butyl
	AFJ	-2-(3-iodopyridyl)	-n-propyl
	AFK	-4-(5-chloropyrimidinyl)	-t-butyl
	AFL	-4-(5-chloropyrimidinyl)	-iso-butyl
15	AFM	-4-(5-chloropyrimidinyl)	-sec-butyl
	AFN	-4-(5-chloropyrimidinyl)	-cyclohexyl
	AFO	-4-(5-chloropyrimidinyl)	-t-butoxy
	AFP	-4-(5-chloropyrimidinyl)	-isopropoxy
	AFQ	-4-(5-chloropyrimidinyl)	-CF ₃
20	AFR	-4-(5-chloropyrimidinyl)	-CH ₂ CF ₃
	AFS	-4-(5-chloropyrimidinyl)	-OCF ₃
	AFT	-4-(5-chloropyrimidinyl)	-Cl
	AFU	-4-(5-chloropyrimidinyl)	-Br
	AFV	-4-(5-chloropyrimidinyl)	-I
25	AFW	-4-(5-chloropyrimidinyl)	-n-butyl
	AFX	-4-(5-chloropyrimidinyl)	-n-propyl
	AFY	-4-(5-methylpyrimidinyl)	-t-butyl
	AFZ	-4-(5-methylpyrimidinyl)	-iso-butyl
	AGA	-4-(5-methylpyrimidinyl)	-sec-butyl
	AGB	-4-(5-methylpyrimidinyl)	-cyclohexyl
	AGC	-4-(5-methylpyrimidinyl)	-t-butoxy
	AGD	-4-(5-methylpyrimidinyl)	-isopropoxy
	AGE	-4-(5-methylpyrimidinyl)	-CF ₃

5	AGF	-4-(5-methylpyrimidinyl)	-CH ₂ CF ₃
	AGG	-4-(5-methylpyrimidinyl)	-OCF ₃
	AGH	-4-(5-methylpyrimidinyl)	-Cl
	AGI	-4-(5-methylpyrimidinyl)	-Br
	AGJ	-4-(5-methylpyrimidinyl)	-I
10	AGK	-4-(5-methylpyrimidinyl)	-n-butyl
	AGL	-4-(5-methylpyrimidinyl)	-n-propyl
	AGM	-4-(5-fluoropyrimidinyl)	-t-butyl
	AGN	-4-(5-fluoropyrimidinyl)	-iso-butyl
	AGO	-4-(5-fluoropyrimidinyl)	-sec-butyl
15	AGP	-4-(5-fluoropyrimidinyl)	-cyclohexyl
	AGQ	-4-(5-fluoropyrimidinyl)	-t-butoxy
	AGR	-4-(5-fluoropyrimidinyl)	-isopropoxy
	AGS	-4-(5-fluoropyrimidinyl)	-CF ₃
	AGT	-4-(5-fluoropyrimidinyl)	-CH ₂ CF ₃
20	AGU	-4-(5-fluoropyrimidinyl)	-OCF ₃
	AGV	-4-(5-fluoropyrimidinyl)	-Cl
	AGW	-4-(5-fluoropyrimidinyl)	-Br
	AGX	-4-(5-fluoropyrimidinyl)	-I
	AGY	-4-(5-fluoropyrimidinyl)	-n-butyl
25	AGZ	-4-(5-fluoropyrimidinyl)	-n-propyl
	AHA	-2-(3-chloropyrazinyl)	-t-butyl
	AHB	-2-(3-chloropyrazinyl)	-iso-butyl
	AHC	-2-(3-chloropyrazinyl)	-sec-butyl
	AHD	-2-(3-chloropyrazinyl)	-cyclohexyl
	AHE	-2-(3-chloropyrazinyl)	-t-butoxy
	AHF	-2-(3-chloropyrazinyl)	-isopropoxy
	AHG	-2-(3-chloropyrazinyl)	-CF ₃
	AHH	-2-(3-chloropyrazinyl)	-CH ₂ CF ₃

5	AHI	-2-(3-chloropyrazinyl)	-OCF ₃
	AHJ	-2-(3-chloropyrazinyl)	-Cl
	AHK	-2-(3-chloropyrazinyl)	-Br
	AHL	-2-(3-chloropyrazinyl)	-I
	AHM	-2-(3-chloropyrazinyl)	-n-butyl
10	AHN	-2-(3-chloropyrazinyl)	-n-propyl
	AHO	-2-(3-methylpyrazinyl)	-t-butyl
	AHP	-2-(3-methylpyrazinyl)	-iso-butyl
	AHQ	-2-(3-methylpyrazinyl)	-sec-butyl
	AHR	-2-(3-methylpyrazinyl)	-cyclohexyl
15	AHS	-2-(3-methylpyrazinyl)	-t-butoxy
	AHT	-2-(3-methylpyrazinyl)	-isopropoxy
	AHU	-2-(3-methylpyrazinyl)	-CF ₃
	AHV	-2-(3-methylpyrazinyl)	-CH ₂ CF ₃
	AHW	-2-(3-methylpyrazinyl)	-OCF ₃
20	AHX	-2-(3-methylpyrazinyl)	-Cl
	AHY	-2-(3-methylpyrazinyl)	-Br
	AHZ	-2-(3-methylpyrazinyl)	-I
	AIA	-2-(3-methylpyrazinyl)	-n-butyl
	AIB	-2-(3-methylpyrazinyl)	-n-propyl
25	AIC	-2-(3-fluoropyrazinyl)	-t-butyl
	AID	-2-(3-fluoropyrazinyl)	-iso-butyl
	AIE	-2-(3-fluoropyrazinyl)	-sec-butyl
	AIF	-2-(3-fluoropyrazinyl)	-cyclohexyl
	AIG	-2-(3-fluoropyrazinyl)	-t-butoxy
	AIH	-2-(3-fluoropyrazinyl)	-isopropoxy
	AII	-2-(3-fluoropyrazinyl)	-CF ₃
	AIJ	-2-(3-fluoropyrazinyl)	-CH ₂ CF ₃
	AIK	-2-(3-fluoropyrazinyl)	-OCF ₃

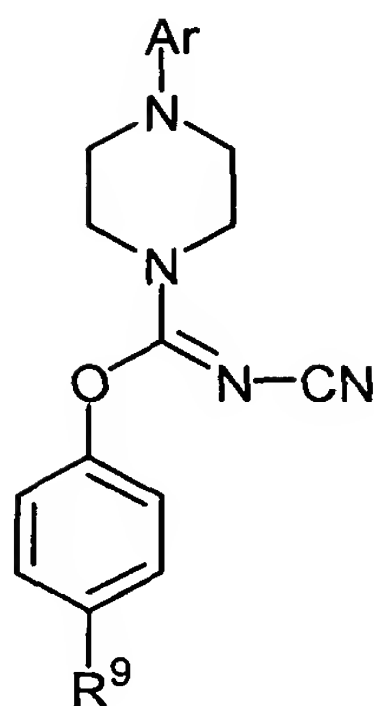
5	AIL	-2-(3-fluoropyrazinyl)	-Cl
	AIM	-2-(3-fluoropyrazinyl)	-Br
	AIN	-2-(3-fluoropyrazinyl)	-I
	AIO	-2-(3-fluoropyrazinyl)	-n-butyl
	AIP	-2-(3-fluoropyrazinyl)	-n-propyl
10	AIQ	-3-(4-chloropyridazinyl)	-t-butyl
	AIR	-3-(4-chloropyridazinyl)	-iso-butyl
	AIS	-3-(4-chloropyridazinyl)	-sec-butyl
	AIT	-3-(4-chloropyridazinyl)	-cyclohexyl
	AIU	-3-(4-chloropyridazinyl)	-t-butoxy
15	AIV	-3-(4-chloropyridazinyl)	-isopropoxy
	AIW	-3-(4-chloropyridazinyl)	-CF ₃
	AIX	-3-(4-chloropyridazinyl)	-CH ₂ CF ₃
	AIY	-3-(4-chloropyridazinyl)	-OCF ₃
	AIZ	-3-(4-chloropyridazinyl)	-Cl
20	AJA	-3-(4-chloropyridazinyl)	-Br
	AJB	-3-(4-chloropyridazinyl)	-I
	AJC	-3-(4-chloropyridazinyl)	-n-butyl
	AJD	-3-(4-chloropyridazinyl)	-n-propyl
	AJE	-3-(4-methylpyridazinyl)	-t-butyl
25	AJF	-3-(4-methylpyridazinyl)	-iso-butyl
	AJG	-3-(4-methylpyridazinyl)	-sec-butyl
	AJH	-3-(4-methylpyridazinyl)	-cyclohexyl
	AJI	-3-(4-methylpyridazinyl)	-t-butoxy
	AJJ	-3-(4-methylpyridazinyl)	-isopropoxy
	AJK	-3-(4-methylpyridazinyl)	-CF ₃
	AJL	-3-(4-methylpyridazinyl)	-CH ₂ CF ₃
	AJM	-3-(4-methylpyridazinyl)	-OCF ₃
	AJN	-3-(4-methylpyridazinyl)	-Cl

5	AJO	-3-(4-methylpyridazinyl)	-Br
	AJP	-3-(4-methylpyridazinyl)	-I
	AJQ	-3-(4-methylpyridazinyl)	-n-butyl
	AJR	-3-(4-methylpyridazinyl)	-n-propyl
	AJS	-3-(4-fluoropyridazinyl)	-t-butyl
10	AJT	-3-(4-fluoropyridazinyl)	-iso-butyl
	AJU	-3-(4-fluoropyridazinyl)	-sec-butyl
	AJV	-3-(4-fluoropyridazinyl)	-cyclohexyl
	AJW	-3-(4-fluoropyridazinyl)	-t-butoxy
	AJX	-3-(4-fluoropyridazinyl)	-isopropoxy
15	AJY	-3-(4-fluoropyridazinyl)	-CF ₃
	AJZ	-3-(4-fluoropyridazinyl)	-CH ₂ CF ₃
	AKA	-3-(4-fluoropyridazinyl)	-OCF ₃
	AKB	-3-(4-fluoropyridazinyl)	-Cl
	AKC	-3-(4-fluoropyridazinyl)	-Br
20	AKD	-3-(4-fluoropyridazinyl)	-I
	AKE	-3-(4-fluoropyridazinyl)	-n-butyl
	AKF	-3-(4-fluoropyridazinyl)	-n-propyl
	AKG	-5-(4-chlorothiadiazolyl)	-t-butyl
	AKH	-5-(4-chlorothiadiazolyl)	-iso-butyl
25	AKI	-5-(4-chlorothiadiazolyl)	-sec-butyl
	AKJ	-5-(4-chlorothiadiazolyl)	-cyclohexyl
	AKK	-5-(4-chlorothiadiazolyl)	-t-butoxy
	AKL	-5-(4-chlorothiadiazolyl)	-isopropoxy
	AKM	-5-(4-chlorothiadiazolyl)	-CF ₃
	AKN	-5-(4-chlorothiadiazolyl)	-CH ₂ CF ₃
	AKO	-5-(4-chlorothiadiazolyl)	-OCF ₃
	AKP	-5-(4-chlorothiadiazolyl)	-Cl
	AKQ	-5-(4-chlorothiadiazolyl)	-Br

5	AKR	-5-(4-chlorothiadiazolyl)	-I
	AKS	-5-(4-chlorothiadiazolyl)	-n-butyl
	AKT	-5-(4-chlorothiadiazolyl)	-n-propyl
	AKU	-5-(4-methylthiadiazolyl)	-t-butyl
	AKV	-5-(4-methylthiadiazolyl)	-iso-butyl
10	AKW	-5-(4-methylthiadiazolyl)	-sec-butyl
	AKX	-5-(4-methylthiadiazolyl)	-cyclohexyl
	AKY	-5-(4-methylthiadiazolyl)	-t-butoxy
	AKZ	-5-(4-methylthiadiazolyl)	-isopropoxy
	ALA	-5-(4-methylthiadiazolyl)	-CF ₃
15	ALB	-5-(4-methylthiadiazolyl)	-CH ₂ CF ₃
	ALC	-5-(4-methylthiadiazolyl)	-OCF ₃
	ALD	-5-(4-methylthiadiazolyl)	-Cl
	ALE	-5-(4-methylthiadiazolyl)	-Br
	ALF	-5-(4-methylthiadiazolyl)	-I
20	ALG	-5-(4-methylthiadiazolyl)	-n-butyl
	ALH	-5-(4-methylthiadiazolyl)	-n-propyl
	ALI	-5-(4-fluorothiadiazolyl)	-t-butyl
	ALJ	-5-(4-fluorothiadiazolyl)	-iso-butyl
	ALK	-5-(4-fluorothiadiazolyl)	-sec-butyl
25	ALL	-5-(4-fluorothiadiazolyl)	-cyclohexyl
	ALM	-5-(4-fluorothiadiazolyl)	-t-butoxy
	ALN	-5-(4-fluorothiadiazolyl)	-isopropoxy
	ALO	-5-(4-fluorothiadiazolyl)	-CF ₃
	ALP	-5-(4-fluorothiadiazolyl)	-CH ₂ CF ₃
	ALQ	-5-(4-fluorothiadiazolyl)	-OCF ₃
	ALR	-5-(4-fluorothiadiazolyl)	-Cl
	ALS	-5-(4-fluorothiadiazolyl)	-Br
	ALT	-5-(4-fluorothiadiazolyl)	-I

ALU	-5-(4-fluorothiadiazolyl)	-n-butyl
ALV	-5-(4-fluorothiadiazolyl)	-n-propyl

Table 2



VII

and pharmaceutically acceptable salts thereof, wherein:

Compound	Ar	R ⁹
ALW	-2-(3-chloropyridyl)	-t-butyl
ALX	-2-(3-chloropyridyl)	-iso-butyl
ALY	-2-(3-chloropyridyl)	-sec-butyl
ALZ	-2-(3-chloropyridyl)	-cyclohexyl
AMA	-2-(3-chloropyridyl)	-t-butoxy
AMB	-2-(3-chloropyridyl)	-isopropoxy
AMC	-2-(3-chloropyridyl)	-CF ₃
AMD	-2-(3-chloropyridyl)	-CH ₂ CF ₃
AME	-2-(3-chloropyridyl)	-OCF ₃
AMF	-2-(3-chloropyridyl)	-Cl
AMG	-2-(3-chloropyridyl)	-Br
AMH	-2-(3-chloropyridyl)	-I
AMI	-2-(3-chloropyridyl)	-n-butyl
AMJ	-2-(3-chloropyridyl)	-n-propyl
AMK	-2-(3-fluoropyridyl)	-t-butyl

5	AML	-2-(3-fluoropyridyl)	-iso-butyl
	AMM	-2-(3-fluoropyridyl)	-sec-butyl
	AMN	-2-(3-fluoropyridyl)	-cyclohexyl
	AMO	-2-(3-fluoropyridyl)	-t-butoxy
	AMP	-2-(3-fluoropyridyl)	-isopropoxy
10	AMQ	-2-(3-fluoropyridyl)	-CF ₃
	AMR	-2-(3-fluoropyridyl)	-CH ₂ CF ₃
	AMS	-2-(3-fluoropyridyl)	-OCF ₃
	AMT	-2-(3-fluoropyridyl)	-Cl
	AMU	-2-(3-fluoropyridyl)	-Br
15	AMV	-2-(3-fluoropyridyl)	-I
	AMW	-2-(3-fluoropyridyl)	-n-butyl
	AMX	-2-(3-fluoropyridyl)	-n-propyl
	AMY	-2-(3-methylpyridyl)	-t-butyl
	AMZ	-2-(3-methylpyridyl)	-iso-butyl
20	ANA	-2-(3-methylpyridyl)	-sec-butyl
	ANB	-2-(3-methylpyridyl)	-cyclohexyl
	ANC	-2-(3-methylpyridyl)	-t-butoxy
	AND	-2-(3-methylpyridyl)	-isopropoxy
	ANE	-2-(3-methylpyridyl)	-CF ₃
25	ANF	-2-(3-methylpyridyl)	-CH ₂ CF ₃
	ANG	-2-(3-methylpyridyl)	-OCF ₃
	ANH	-2-(3-methylpyridyl)	-Cl
	ANI	-2-(3-methylpyridyl)	-Br
	ANJ	-2-(3-methylpyridyl)	-I
	ANK	-2-(3-methylpyridyl)	-n-butyl
	ANL	-2-(3-methylpyridyl)	-n-propyl
	ANM	-2-(3-CF ₃ -pyridyl)	-t-butyl
	ANN	-2-(3-CF ₃ -pyridyl)	-iso-butyl

5	ANO	-2-(3-CF ₃ -pyridyl)	-sec-butyl
	ANP	-2-(3-CF ₃ -pyridyl)	-cyclohexyl
	ANQ	-2-(3-CF ₃ -pyridyl)	-t-butoxy
	ANR	-2-(3-CF ₃ -pyridyl)	-isopropoxy
	ANS	-2-(3-CF ₃ -pyridyl)	-CF ₃
10	ANT	-2-(3-CF ₃ -pyridyl)	-CH ₂ CF ₃
	ANU	-2-(3-CF ₃ -pyridyl)	-OCF ₃
	ANV	-2-(3-CF ₃ -pyridyl)	-Cl
	ANW	-2-(3-CF ₃ -pyridyl)	-Br
	ANX	-2-(3-CF ₃ -pyridyl)	-I
15	ANY	-2-(3-CF ₃ -pyridyl)	-n-butyl
	ANZ	-2-(3-CF ₃ -pyridyl)	-n-propyl
	AOA	-2-(3-CHF ₂ -pyridyl)	-t-butyl
	AOB	-2-(3-CHF ₂ -pyridyl)	-iso-butyl
	AOC	-2-(3-CHF ₂ -pyridyl)	-sec-butyl
20	AOD	-2-(3-CHF ₂ -pyridyl)	-cyclohexyl
	AOE	-2-(3-CHF ₂ -pyridyl)	-t-butoxy
	AOF	-2-(3-CHF ₂ -pyridyl)	-isopropoxy
	AOG	-2-(3-CHF ₂ -pyridyl)	-CF ₃
	AOH	-2-(3-CHF ₂ -pyridyl)	-CH ₂ CF ₃
25	AOI	-2-(3-CHF ₂ -pyridyl)	-OCF ₃
	AOJ	-2-(3-CHF ₂ -pyridyl)	-Cl
	AOK	-2-(3-CHF ₂ -pyridyl)	-Br
	AOL	-2-(3-CHF ₂ -pyridyl)	-I
	AOM	-2-(3-CHF ₂ -pyridyl)	-n-butyl
	AON	-2-(3-CHF ₂ -pyridyl)	-n-propyl
	AOO	-2-(3-hydroxypyridyl)	-t-butyl
	AOP	-2-(3-hydroxypyridyl)	-iso-butyl
	AOQ	-2-(3-hydroxypyridyl)	-sec-butyl

5	AOR	-2-(3-hydroxypyridyl)	-cyclohexyl
	AOS	-2-(3-hydroxypyridyl)	-t-butoxy
	AOT	-2-(3-hydroxypyridyl)	-isopropoxy
	AOU	-2-(3-hydroxypyridyl)	-CF ₃
	AOV	-2-(3-hydroxypyridyl)	-CH ₂ CF ₃
	AOW	-2-(3-hydroxypyridyl)	-OCF ₃
	AOX	-2-(3-hydroxypyridyl)	-Cl
	AOY	-2-(3-hydroxypyridyl)	-Br
	AOZ	-2-(3-hydroxypyridyl)	-I
10	APA	-2-(3-hydroxypyridyl)	-n-butyl
	APB	-2-(3-hydroxypyridyl)	-n-propyl
	APC	-2-(3-nitropyridyl)	-t-butyl
	APD	-2-(3-nitropyridyl)	-iso-butyl
15	APE	-2-(3-nitropyridyl)	-sec-butyl
	APF	-2-(3-nitropyridyl)	-cyclohexyl
	APG	-2-(3-nitropyridyl)	-t-butoxy
	APH	-2-(3-nitropyridyl)	-isopropoxy
	API	-2-(3-nitropyridyl)	-CF ₃
	APJ	-2-(3-nitropyridyl)	-CH ₂ CF ₃
	APK	-2-(3-nitropyridyl)	-OCF ₃
20	APL	-2-(3-nitropyridyl)	-Cl
	APM	-2-(3-nitropyridyl)	-Br
	APN	-2-(3-nitropyridyl)	-I
	APO	-2-(3-nitropyridyl)	-n-butyl
25	APP	-2-(3-nitropyridyl)	-n-propyl
	APQ	-2-(3-cyanopyridyl)	-t-butyl
	APR	-2-(3-cyanopyridyl)	-iso-butyl
	APS	-2-(3-cyanopyridyl)	-sec-butyl
	APT	-2-(3-cyanopyridyl)	-cyclohexyl

5	APU	-2-(3-cyanopyridyl)	-t-butoxy
	APV	-2-(3-cyanopyridyl)	-isopropoxy
	APW	-2-(3-cyanopyridyl)	-CF ₃
	APX	-2-(3-cyanopyridyl)	-CH ₂ CF ₃
	APY	-2-(3-cyanopyridyl)	-OCF ₃
10	APZ	-2-(3-cyanopyridyl)	-Cl
	AQA	-2-(3-cyanopyridyl)	-Br
	AQB	-2-(3-cyanopyridyl)	-I
	AQC	-2-(3-cyanopyridyl)	-n-butyl
	AQD	-2-(3-cyanopyridyl)	-n-propyl
15	AQE	-2-(3-bromopyridyl)	-t-butyl
	AQF	-2-(3-bromopyridyl)	-iso-butyl
	AQG	-2-(3-bromopyridyl)	-sec-butyl
	AQH	-2-(3-bromopyridyl)	-cyclohexyl
	AQI	-2-(3-bromopyridyl)	-t-butoxy
20	AQJ	-2-(3-bromopyridyl)	-isopropoxy
	AQK	-2-(3-bromopyridyl)	-CF ₃
	AQL	-2-(3-bromopyridyl)	-CH ₂ CF ₃
	AQM	-2-(3-bromopyridyl)	-OCF ₃
	AQN	-2-(3-bromopyridyl)	-Cl
25	AQO	-2-(3-bromopyridyl)	-Br
	AQP	-2-(3-bromopyridyl)	-I
	AQQ	-2-(3-bromopyridyl)	-n-butyl
	AQR	-2-(3-bromopyridyl)	-n-propyl
	AQS	-2-(3-iodopyridyl)	-t-butyl
	AQT	-2-(3-iodopyridyl)	-iso-butyl
	AQU	-2-(3-iodopyridyl)	-sec-butyl
	AQV	-2-(3-iodopyridyl)	-cyclohexyl
	AQW	-2-(3-iodopyridyl)	-t-butoxy

5	AQX	-2-(3-iodopyridyl)	-isopropoxy
	AQY	-2-(3-iodopyridyl)	-CF ₃
	AQZ	-2-(3-iodopyridyl)	-CH ₂ CF ₃
	ARA	-2-(3-iodopyridyl)	-OCF ₃
	ARB	-2-(3-iodopyridyl)	-Cl
10	ARC	-2-(3-iodopyridyl)	-Br
	ARD	-2-(3-iodopyridyl)	-I
	ARE	-2-(3-iodopyridyl)	-n-butyl
	ARF	-2-(3-iodopyridyl)	-n-propyl
	ARG	-4-(5-chloropyrimidinyl)	-t-butyl
15	ARH	-4-(5-chloropyrimidinyl)	-iso-butyl
	ARI	-4-(5-chloropyrimidinyl)	-sec-butyl
	ARJ	-4-(5-chloropyrimidinyl)	-cyclohexyl
	ARK	-4-(5-chloropyrimidinyl)	-t-butoxy
	ARL	-4-(5-chloropyrimidinyl)	-isopropoxy
20	ARM	-4-(5-chloropyrimidinyl)	-CF ₃
	ARN	-4-(5-chloropyrimidinyl)	-CH ₂ CF ₃
	ARO	-4-(5-chloropyrimidinyl)	-OCF ₃
	ARP	-4-(5-chloropyrimidinyl)	-Cl
	ARQ	-4-(5-chloropyrimidinyl)	-Br
25	ARR	-4-(5-chloropyrimidinyl)	-I
	ARS	-4-(5-chloropyrimidinyl)	-n-butyl
	ART	-4-(5-chloropyrimidinyl)	-n-propyl
	ARU	-4-(5-methylpyrimidinyl)	-t-butyl
	ARV	-4-(5-methylpyrimidinyl)	-iso-butyl
	ARW	-4-(5-methylpyrimidinyl)	-sec-butyl
	ARX	-4-(5-methylpyrimidinyl)	-cyclohexyl
	ARY	-4-(5-methylpyrimidinyl)	-t-butoxy
	ARZ	-4-(5-methylpyrimidinyl)	-isopropoxy

5	ASA	-4-(5-methylpyrimidinyl)	-CF ₃
	ASB	-4-(5-methylpyrimidinyl)	-CH ₂ CF ₃
	ASC	-4-(5-methylpyrimidinyl)	-OCF ₃
	ASD	-4-(5-methylpyrimidinyl)	-Cl
	ASE	-4-(5-methylpyrimidinyl)	-Br
10	ASF	-4-(5-methylpyrimidinyl)	-I
	ASG	-4-(5-methylpyrimidinyl)	-n-butyl
	ASH	-4-(5-methylpyrimidinyl)	-n-propyl
	ASI	-4-(5-fluoropyrimidinyl)	-t-butyl
	ASJ	-4-(5-fluoropyrimidinyl)	-iso-butyl
15	ASK	-4-(5-fluoropyrimidinyl)	-sec-butyl
	ASL	-4-(5-fluoropyrimidinyl)	-cyclohexyl
	ASM	-4-(5-fluoropyrimidinyl)	-t-butoxy
	ASN	-4-(5-fluoropyrimidinyl)	-isopropoxy
	ASO	-4-(5-fluoropyrimidinyl)	-CF ₃
20	ASP	-4-(5-fluoropyrimidinyl)	-CH ₂ CF ₃
	ASQ	-4-(5-fluoropyrimidinyl)	-OCF ₃
	ASR	-4-(5-fluoropyrimidinyl)	-Cl
	ASS	-4-(5-fluoropyrimidinyl)	-Br
	AST	-4-(5-fluoropyrimidinyl)	-I
25	ASU	-4-(5-fluoropyrimidinyl)	-n-butyl
	ASV	-4-(5-fluoropyrimidinyl)	-n-propyl
	ASW	-2-(3-chloropyrazinyl)	-t-butyl
	ASX	-2-(3-chloropyrazinyl)	-iso-butyl
	ASY	-2-(3-chloropyrazinyl)	-sec-butyl
	ASZ	-2-(3-chloropyrazinyl)	-cyclohexyl
	ATA	-2-(3-chloropyrazinyl)	-t-butoxy
	ATB	-2-(3-chloropyrazinyl)	-isopropoxy
	ATC	-2-(3-chloropyrazinyl)	-CF ₃

5	ATD	-2-(3-chloropyrazinyl)	-CH ₂ CF ₃
	ATE	-2-(3-chloropyrazinyl)	-OCF ₃
	ATF	-2-(3-chloropyrazinyl)	-Cl
	ATG	-2-(3-chloropyrazinyl)	-Br
	ATH	-2-(3-chloropyrazinyl)	-I
10	ATI	-2-(3-chloropyrazinyl)	-n-butyl
	ATJ	-2-(3-chloropyrazinyl)	-n-propyl
	ATK	-2-(3-methylpyrazinyl)	-t-butyl
	ATL	-2-(3-methylpyrazinyl)	-iso-butyl
	ATM	-2-(3-methylpyrazinyl)	-sec-butyl
15	ATN	-2-(3-methylpyrazinyl)	-cyclohexyl
	ATO	-2-(3-methylpyrazinyl)	-t-butoxy
	ATP	-2-(3-methylpyrazinyl)	-isopropoxy
	ATQ	-2-(3-methylpyrazinyl)	-CF ₃
	ATR	-2-(3-methylpyrazinyl)	-CH ₂ CF ₃
20	ATS	-2-(3-methylpyrazinyl)	-OCF ₃
	ATT	-2-(3-methylpyrazinyl)	-Cl
	ATU	-2-(3-methylpyrazinyl)	-Br
	ATV	-2-(3-methylpyrazinyl)	-I
	ATW	-2-(3-methylpyrazinyl)	-n-butyl
25	ATX	-2-(3-methylpyrazinyl)	-n-propyl
	ATY	-2-(3-fluoropyrazinyl)	-t-butyl
	ATZ	-2-(3-fluoropyrazinyl)	-iso-butyl
	AUA	-2-(3-fluoropyrazinyl)	-sec-butyl
	AUB	-2-(3-fluoropyrazinyl)	-cyclohexyl
	AUC	-2-(3-fluoropyrazinyl)	-t-butoxy
	AUD	-2-(3-fluoropyrazinyl)	-isopropoxy
	AUE	-2-(3-fluoropyrazinyl)	-CF ₃
	AUF	-2-(3-fluoropyrazinyl)	-CH ₂ CF ₃

5	AUG	-2-(3-fluoropyrazinyl)	-OCF ₃
	AUH	-2-(3-fluoropyrazinyl)	-Cl
	AUI	-2-(3-fluoropyrazinyl)	-Br
	AUJ	-2-(3-fluoropyrazinyl)	-I
	AUK	-2-(3-fluoropyrazinyl)	-n-butyl
10	AUL	-2-(3-fluoropyrazinyl)	-n-propyl
	AUM	-3-(4-chloropyridazinyl)	-t-butyl
	AUN	-3-(4-chloropyridazinyl)	-iso-butyl
	AUO	-3-(4-chloropyridazinyl)	-sec-butyl
	AUP	-3-(4-chloropyridazinyl)	-cyclohexyl
15	AUQ	-3-(4-chloropyridazinyl)	-t-butoxy
	AUR	-3-(4-chloropyridazinyl)	-isopropoxy
	AUS	-3-(4-chloropyridazinyl)	-CF ₃
	AUT	-3-(4-chloropyridazinyl)	-CH ₂ CF ₃
	AUU	-3-(4-chloropyridazinyl)	-OCF ₃
20	AUV	-3-(4-chloropyridazinyl)	-Cl
	AUW	-3-(4-chloropyridazinyl)	-Br
	AUX	-3-(4-chloropyridazinyl)	-I
	AUY	-3-(4-chloropyridazinyl)	-n-butyl
	AUZ	-3-(4-chloropyridazinyl)	-n-propyl
25	AVA	-3-(4-methylpyridazinyl)	-t-butyl
	AVB	-3-(4-methylpyridazinyl)	-iso-butyl
	AVC	-3-(4-methylpyridazinyl)	-sec-butyl
	AVD	-3-(4-methylpyridazinyl)	-cyclohexyl
	AVE	-3-(4-methylpyridazinyl)	-t-butoxy
	AVF	-3-(4-methylpyridazinyl)	-isopropoxy
	AVG	-3-(4-methylpyridazinyl)	-CF ₃
	AVH	-3-(4-methylpyridazinyl)	-CH ₂ CF ₃
	AVI	-3-(4-methylpyridazinyl)	-OCF ₃

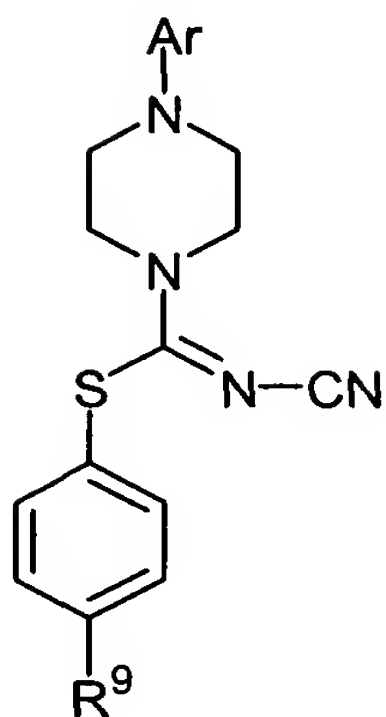
5	AVJ	-3-(4-methylpyridazinyl)	-Cl
	AVK	-3-(4-methylpyridazinyl)	-Br
	AVL	-3-(4-methylpyridazinyl)	-I
	AVM	-3-(4-methylpyridazinyl)	-n-butyl
	AVN	-3-(4-methylpyridazinyl)	-n-propyl
10	AVO	-3-(4-fluoropyridazinyl)	-t-butyl
	AVP	-3-(4-fluoropyridazinyl)	-iso-butyl
	AVQ	-3-(4-fluoropyridazinyl)	-sec-butyl
	AVR	-3-(4-fluoropyridazinyl)	-cyclohexyl
	AVS	-3-(4-fluoropyridazinyl)	-t-butoxy
15	AVT	-3-(4-fluoropyridazinyl)	-isopropoxy
	AVU	-3-(4-fluoropyridazinyl)	-CF ₃
	AVV	-3-(4-fluoropyridazinyl)	-CH ₂ CF ₃
	AVW	-3-(4-fluoropyridazinyl)	-OCF ₃
	AVX	-3-(4-fluoropyridazinyl)	-Cl
20	AVY	-3-(4-fluoropyridazinyl)	-Br
	AVZ	-3-(4-fluoropyridazinyl)	-I
	AWA	-3-(4-fluoropyridazinyl)	-n-butyl
	AWB	-3-(4-fluoropyridazinyl)	-n-propyl
	AWC	-5-(4-chlorothiadiazolyl)	-t-butyl
25	AWD	-5-(4-chlorothiadiazolyl)	-iso-butyl
	AWE	-5-(4-chlorothiadiazolyl)	-sec-butyl
	AWF	-5-(4-chlorothiadiazolyl)	-cyclohexyl
	AWG	-5-(4-chlorothiadiazolyl)	-t-butoxy
	AWH	-5-(4-chlorothiadiazolyl)	-isopropoxy
	AWI	-5-(4-chlorothiadiazolyl)	-CF ₃
	AWJ	-5-(4-chlorothiadiazolyl)	-CH ₂ CF ₃
	AWK	-5-(4-chlorothiadiazolyl)	-OCF ₃
	AWL	-5-(4-chlorothiadiazolyl)	-Cl

5	AWM	-5-(4-chlorothiadiazolyl)	-Br
	AWN	-5-(4-chlorothiadiazolyl)	-I
	AWO	-5-(4-chlorothiadiazolyl)	-n-butyl
	AWP	-5-(4-chlorothiadiazolyl)	-n-propyl
	AWQ	-5-(4-methylthiadiazolyl)	-t-butyl
10	AWR	-5-(4-methylthiadiazolyl)	-iso-butyl
	AWS	-5-(4-methylthiadiazolyl)	-sec-butyl
	AWT	-5-(4-methylthiadiazolyl)	-cyclohexyl
	AWU	-5-(4-methylthiadiazolyl)	-t-butoxy
	AWV	-5-(4-methylthiadiazolyl)	-isopropoxy
15	AWW	-5-(4-methylthiadiazolyl)	-CF ₃
	AWX	-5-(4-methylthiadiazolyl)	-CH ₂ CF ₃
	AWY	-5-(4-methylthiadiazolyl)	-OCF ₃
	AWZ	-5-(4-methylthiadiazolyl)	-Cl
	AXA	-5-(4-methylthiadiazolyl)	-Br
20	AXB	-5-(4-methylthiadiazolyl)	-I
	AXC	-5-(4-methylthiadiazolyl)	-n-butyl
	AXD	-5-(4-methylthiadiazolyl)	-n-propyl
	AXE	-5-(4-fluorothiadiazolyl)	-t-butyl
	AXF	-5-(4-fluorothiadiazolyl)	-iso-butyl
25	AXG	-5-(4-fluorothiadiazolyl)	-sec-butyl
	AXH	-5-(4-fluorothiadiazolyl)	-cyclohexyl
	AXI	-5-(4-fluorothiadiazolyl)	-t-butoxy
	AXJ	-5-(4-fluorothiadiazolyl)	-isopropoxy
	AXK	-5-(4-fluorothiadiazolyl)	-CF ₃
	AXL	-5-(4-fluorothiadiazolyl)	-CH ₂ CF ₃
	AXM	-5-(4-fluorothiadiazolyl)	-OCF ₃
	AXN	-5-(4-fluorothiadiazolyl)	-Cl
	AXO	-5-(4-fluorothiadiazolyl)	-Br

AXP	-5-(4-fluorothiadiazolyl)	-I
AXQ	-5-(4-fluorothiadiazolyl)	-n-butyl
AXR	-5-(4-fluorothiadiazolyl)	-n-propyl

5

Table 3



VIII

and pharmaceutically acceptable salts thereof, wherein:

Compound	Ar	R ⁹
AXS	-2-(3-chloropyridyl)	-t-butyl
AXT	-2-(3-chloropyridyl)	-iso-butyl
AXU	-2-(3-chloropyridyl)	-sec-butyl
AXV	-2-(3-chloropyridyl)	-cyclohexyl
AXW	-2-(3-chloropyridyl)	-t-butoxy
AXX	-2-(3-chloropyridyl)	-isopropoxy
AXY	-2-(3-chloropyridyl)	-CF ₃
AXZ	-2-(3-chloropyridyl)	-CH ₂ CF ₃
AYA	-2-(3-chloropyridyl)	-OCF ₃
AYB	-2-(3-chloropyridyl)	-Cl
AYC	-2-(3-chloropyridyl)	-Br
AYD	-2-(3-chloropyridyl)	-I
AYE	-2-(3-chloropyridyl)	-n-butyl
AYF	-2-(3-chloropyridyl)	-n-propyl
AYG	-2-(3-fluoropyridyl)	-t-butyl

5	AYH	-2-(3-fluoropyridyl)	-iso-butyl
	AYI	-2-(3-fluoropyridyl)	-sec-butyl
	AYJ	-2-(3-fluoropyridyl)	-cyclohexyl
	AYK	-2-(3-fluoropyridyl)	-t-butoxy
	AYL	-2-(3-fluoropyridyl)	-isopropoxy
10	AYM	-2-(3-fluoropyridyl)	-CF ₃
	AYN	-2-(3-fluoropyridyl)	-CH ₂ CF ₃
	AYO	-2-(3-fluoropyridyl)	-OCF ₃
	AYP	-2-(3-fluoropyridyl)	-Cl
	AYQ	-2-(3-fluoropyridyl)	-Br
15	AYR	-2-(3-fluoropyridyl)	-I
	AYS	-2-(3-fluoropyridyl)	-n-butyl
	AYT	-2-(3-fluoropyridyl)	-n-propyl
	AYU	-2-(3-methylpyridyl)	-t-butyl
	AYV	-2-(3-methylpyridyl)	-iso-butyl
20	AYW	-2-(3-methylpyridyl)	-sec-butyl
	AYX	-2-(3-methylpyridyl)	-cyclohexyl
	AYY	-2-(3-methylpyridyl)	-t-butoxy
	AYZ	-2-(3-methylpyridyl)	-isopropoxy
	AZA	-2-(3-methylpyridyl)	-CF ₃
25	AZB	-2-(3-methylpyridyl)	-CH ₂ CF ₃
	AZC	-2-(3-methylpyridyl)	-OCF ₃
	AZD	-2-(3-methylpyridyl)	-Cl
	AZE	-2-(3-methylpyridyl)	-Br
	AZF	-2-(3-methylpyridyl)	-I
	AZG	-2-(3-methylpyridyl)	-n-butyl
	AZH	-2-(3-methylpyridyl)	-n-propyl
	AZI	-2-(3-CF ₃ -pyridyl)	-t-butyl
	AZJ	-2-(3-CF ₃ -pyridyl)	-iso-butyl

5	AZK	-2-(3-CF ₃ -pyridyl)	-sec-butyl
	AZL	-2-(3-CF ₃ -pyridyl)	-cyclohexyl
	AZM	-2-(3-CF ₃ -pyridyl)	-t-butoxy
	AZN	-2-(3-CF ₃ -pyridyl)	-isopropoxy
	AZO	-2-(3-CF ₃ -pyridyl)	-CF ₃
10	AZP	-2-(3-CF ₃ -pyridyl)	-CH ₂ CF ₃
	AZQ	-2-(3-CF ₃ -pyridyl)	-OCF ₃
	AZR	-2-(3-CF ₃ -pyridyl)	-Cl
	AZS	-2-(3-CF ₃ -pyridyl)	-Br
	AZT	-2-(3-CF ₃ -pyridyl)	-I
15	AZU	-2-(3-CF ₃ -pyridyl)	-n-butyl
	AZV	-2-(3-CF ₃ -pyridyl)	-n-propyl
	AZW	-2-(3-CHF ₂ -pyridyl)	-t-butyl
	AZX	-2-(3-CHF ₂ -pyridyl)	-iso-butyl
	AZY	-2-(3-CHF ₂ -pyridyl)	-sec-butyl
20	AZZ	-2-(3-CHF ₂ -pyridyl)	-cyclohexyl
	BAA	-2-(3-CHF ₂ -pyridyl)	-t-butoxy
	BAB	-2-(3-CHF ₂ -pyridyl)	-isopropoxy
	BAC	-2-(3-CHF ₂ -pyridyl)	-CF ₃
	BAD	-2-(3-CHF ₂ -pyridyl)	-CH ₂ CF ₃
25	BAE	-2-(3-CHF ₂ -pyridyl)	-OCF ₃
	BAF	-2-(3-CHF ₂ -pyridyl)	-Cl
	BAG	-2-(3-CHF ₂ -pyridyl)	-Br
	BAH	-2-(3-CHF ₂ -pyridyl)	-I
	BAI	-2-(3-CHF ₂ -pyridyl)	-n-butyl
	BAJ	-2-(3-CHF ₂ -pyridyl)	-n-propyl
	BAK	-2-(3-hydroxypyridyl)	-t-butyl
	BAL	-2-(3-hydroxypyridyl)	-iso-butyl
	BAM	-2-(3-hydroxypyridyl)	-sec-butyl

5	BAN	-2-(3-hydroxypyridyl)	-cyclohexyl
	BAO	-2-(3-hydroxypyridyl)	-t-butoxy
	BAP	-2-(3-hydroxypyridyl)	-isopropoxy
	BAQ	-2-(3-hydroxypyridyl)	-CF ₃
	BAR	-2-(3-hydroxypyridyl)	-CH ₂ CF ₃
10	BAS	-2-(3-hydroxypyridyl)	-OCF ₃
	BAT	-2-(3-hydroxypyridyl)	-Cl
	BAU	-2-(3-hydroxypyridyl)	-Br
	BAV	-2-(3-hydroxypyridyl)	-I
	BAW	-2-(3-hydroxypyridyl)	-n-butyl
15	BAX	-2-(3-hydroxypyridyl)	-n-propyl
	BAY	-2-(3-nitropyridyl)	-t-butyl
	BAZ	-2-(3-nitropyridyl)	-iso-butyl
	BBA	-2-(3-nitropyridyl)	-sec-butyl
	BBB	-2-(3-nitropyridyl)	-cyclohexyl
20	BBC	-2-(3-nitropyridyl)	-t-butoxy
	BBD	-2-(3-nitropyridyl)	-isopropoxy
	BBE	-2-(3-nitropyridyl)	-CF ₃
	BBF	-2-(3-nitropyridyl)	-CH ₂ CF ₃
	BBG	-2-(3-nitropyridyl)	-OCF ₃
25	BBH	-2-(3-nitropyridyl)	-Cl
	BBI	-2-(3-nitropyridyl)	-Br
	BBJ	-2-(3-nitropyridyl)	-I
	BBK	-2-(3-nitropyridyl)	-n-butyl
	BBL	-2-(3-nitropyridyl)	-n-propyl
	BBM	-2-(3-cyanopyridyl)	-t-butyl
	BBN	-2-(3-cyanopyridyl)	-iso-butyl
	BBO	-2-(3-cyanopyridyl)	-sec-butyl
	BBP	-2-(3-cyanopyridyl)	-cyclohexyl

5	BBQ	-2-(3-cyanopyridyl)	-t-butoxy
	BBR	-2-(3-cyanopyridyl)	-isopropoxy
	BBS	-2-(3-cyanopyridyl)	-CF ₃
	BBT	-2-(3-cyanopyridyl)	-CH ₂ CF ₃
	BBU	-2-(3-cyanopyridyl)	-OCF ₃
10	BBV	-2-(3-cyanopyridyl)	-Cl
	BBW	-2-(3-cyanopyridyl)	-Br
	BBX	-2-(3-cyanopyridyl)	-I
	BBY	-2-(3-cyanopyridyl)	-n-butyl
	BBZ	-2-(3-cyanopyridyl)	-n-propyl
15	BCA	-2-(3-bromopyridyl)	-t-butyl
	BCB	-2-(3-bromopyridyl)	-iso-butyl
	BCC	-2-(3-bromopyridyl)	-sec-butyl
	BCD	-2-(3-bromopyridyl)	-cyclohexyl
	BCE	-2-(3-bromopyridyl)	-t-butoxy
20	BCF	-2-(3-bromopyridyl)	-isopropoxy
	BCG	-2-(3-bromopyridyl)	-CF ₃
	BCH	-2-(3-bromopyridyl)	-CH ₂ CF ₃
	BCI	-2-(3-bromopyridyl)	-OCF ₃
	BCJ	-2-(3-bromopyridyl)	-Cl
25	BCK	-2-(3-bromopyridyl)	-Br
	BCL	-2-(3-bromopyridyl)	-I
	BCM	-2-(3-bromopyridyl)	-n-butyl
	BCN	-2-(3-bromopyridyl)	-n-propyl
	BCO	-2-(3-iodopyridyl)	-t-butyl
	BCP	-2-(3-iodopyridyl)	-iso-butyl
	BCQ	-2-(3-iodopyridyl)	-sec-butyl
	BCR	-2-(3-iodopyridyl)	-cyclohexyl
	BCS	-2-(3-iodopyridyl)	-t-butoxy

5	BCT	-2-(3-iodopyridyl)	-isopropoxy
	BCU	-2-(3-iodopyridyl)	-CF ₃
	BCV	-2-(3-iodopyridyl)	-CH ₂ CF ₃
	BCW	-2-(3-iodopyridyl)	-OCF ₃
	BCX	-2-(3-iodopyridyl)	-Cl
10	BCY	-2-(3-iodopyridyl)	-Br
	BCZ	-2-(3-iodopyridyl)	-I
	BDA	-2-(3-iodopyridyl)	-n-butyl
	BDB	-2-(3-iodopyridyl)	-n-propyl
	BDC	-4-(5-chloropyrimidinyl)	-t-butyl
15	BDD	-4-(5-chloropyrimidinyl)	-iso-butyl
	BDE	-4-(5-chloropyrimidinyl)	-sec-butyl
	BDF	-4-(5-chloropyrimidinyl)	-cyclohexyl
	BDG	-4-(5-chloropyrimidinyl)	-t-butoxy
	BDH	-4-(5-chloropyrimidinyl)	-isopropoxy
20	BDI	-4-(5-chloropyrimidinyl)	-CF ₃
	BDJ	-4-(5-chloropyrimidinyl)	-CH ₂ CF ₃
	BDK	-4-(5-chloropyrimidinyl)	-OCF ₃
	BDL	-4-(5-chloropyrimidinyl)	-Cl
	BDM	-4-(5-chloropyrimidinyl)	-Br
25	BDN	-4-(5-chloropyrimidinyl)	-I
	BDO	-4-(5-chloropyrimidinyl)	-n-butyl
	BDP	-4-(5-chloropyrimidinyl)	-n-propyl
	BDQ	-4-(5-methylpyrimidinyl)	-t-butyl
	BDR	-4-(5-methylpyrimidinyl)	-iso-butyl
	BDS	-4-(5-methylpyrimidinyl)	-sec-butyl
	BDT	-4-(5-methylpyrimidinyl)	-cyclohexyl
	BDU	-4-(5-methylpyrimidinyl)	-t-butoxy
	BDV	-4-(5-methylpyrimidinyl)	-isopropoxy

	BDW	-4-(5-methylpyrimidinyl)	-CF ₃
	BDX	-4-(5-methylpyrimidinyl)	-CH ₂ CF ₃
	BDY	-4-(5-methylpyrimidinyl)	-OCF ₃
	BDZ	-4-(5-methylpyrimidinyl)	-Cl
5	BEA	-4-(5-methylpyrimidinyl)	-Br
	BEB	-4-(5-methylpyrimidinyl)	-I
	BEC	-4-(5-methylpyrimidinyl)	-n-butyl
	BED	-4-(5-methylpyrimidinyl)	-n-propyl
	BEE	-4-(5-fluoropyrimidinyl)	-t-butyl
10	BEF	-4-(5-fluoropyrimidinyl)	-iso-butyl
	BEG	-4-(5-fluoropyrimidinyl)	-sec-butyl
	BEH	-4-(5-fluoropyrimidinyl)	-cyclohexyl
	BEI	-4-(5-fluoropyrimidinyl)	-t-butoxy
	BEJ	-4-(5-fluoropyrimidinyl)	-isopropoxy
15	BEK	-4-(5-fluoropyrimidinyl)	-CF ₃
	BEL	-4-(5-fluoropyrimidinyl)	-CH ₂ CF ₃
	BEM	-4-(5-fluoropyrimidinyl)	-OCF ₃
	BEN	-4-(5-fluoropyrimidinyl)	-Cl
	BEO	-4-(5-fluoropyrimidinyl)	-Br
20	BEP	-4-(5-fluoropyrimidinyl)	-I
	BEQ	-4-(5-fluoropyrimidinyl)	-n-butyl
	BER	-4-(5-fluoropyrimidinyl)	-n-propyl
	BES	-2-(3-chloropyrazinyl)	-t-butyl
	BET	-2-(3-chloropyrazinyl)	-iso-butyl
25	BEU	-2-(3-chloropyrazinyl)	-sec-butyl
	BEV	-2-(3-chloropyrazinyl)	-cyclohexyl
	BEW	-2-(3-chloropyrazinyl)	-t-butoxy
	BEX	-2-(3-chloropyrazinyl)	-isopropoxy
	BEY	-2-(3-chloropyrazinyl)	-CF ₃

5	BEZ	-2-(3-chloropyrazinyl)	-CH ₂ CF ₃
	BFA	-2-(3-chloropyrazinyl)	-OCF ₃
	BFB	-2-(3-chloropyrazinyl)	-Cl
	BFC	-2-(3-chloropyrazinyl)	-Br
	BFD	-2-(3-chloropyrazinyl)	-I
10	BFE	-2-(3-chloropyrazinyl)	-n-butyl
	BFF	-2-(3-chloropyrazinyl)	-n-propyl
	BFG	-2-(3-methylpyrazinyl)	-t-butyl
	BFH	-2-(3-methylpyrazinyl)	-iso-butyl
	BFI	-2-(3-methylpyrazinyl)	-sec-butyl
15	BFJ	-2-(3-methylpyrazinyl)	-cyclohexyl
	BFK	-2-(3-methylpyrazinyl)	-t-butoxy
	BFL	-2-(3-methylpyrazinyl)	-isopropoxy
	BFM	-2-(3-methylpyrazinyl)	-CF ₃
	BFN	-2-(3-methylpyrazinyl)	-CH ₂ CF ₃
20	BFO	-2-(3-methylpyrazinyl)	-OCF ₃
	BFP	-2-(3-methylpyrazinyl)	-Cl
	BFQ	-2-(3-methylpyrazinyl)	-Br
	BFR	-2-(3-methylpyrazinyl)	-I
	BFS	-2-(3-methylpyrazinyl)	-n-butyl
25	BFT	-2-(3-methylpyrazinyl)	-n-propyl
	BFU	-2-(3-fluoropyrazinyl)	-t-butyl
	BFV	-2-(3-fluoropyrazinyl)	-iso-butyl
	BFW	-2-(3-fluoropyrazinyl)	-sec-butyl
	BFX	-2-(3-fluoropyrazinyl)	-cyclohexyl
	BFY	-2-(3-fluoropyrazinyl)	-t-butoxy
	BFZ	-2-(3-fluoropyrazinyl)	-isopropoxy
	BGA	-2-(3-fluoropyrazinyl)	-CF ₃
	BGB	-2-(3-fluoropyrazinyl)	-CH ₂ CF ₃

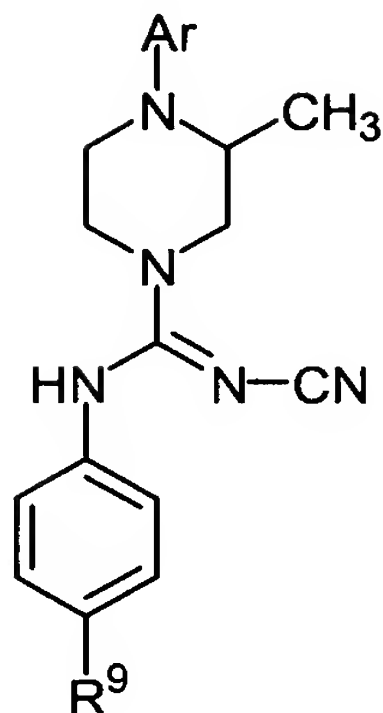
5	BGC	-2-(3-fluoropyrazinyl)	-OCF ₃
	BGD	-2-(3-fluoropyrazinyl)	-Cl
	BGE	-2-(3-fluoropyrazinyl)	-Br
	BGF	-2-(3-fluoropyrazinyl)	-I
	BGG	-2-(3-fluoropyrazinyl)	-n-butyl
10	BGH	-2-(3-fluoropyrazinyl)	-n-propyl
	BGI	-3-(4-chloropyridazinyl)	-t-butyl
	BGJ	-3-(4-chloropyridazinyl)	-iso-butyl
	BGK	-3-(4-chloropyridazinyl)	-sec-butyl
	BGL	-3-(4-chloropyridazinyl)	-cyclohexyl
15	BGM	-3-(4-chloropyridazinyl)	-t-butoxy
	BGN	-3-(4-chloropyridazinyl)	-isopropoxy
	BGO	-3-(4-chloropyridazinyl)	-CF ₃
	BGP	-3-(4-chloropyridazinyl)	-CH ₂ CF ₃
	BGQ	-3-(4-chloropyridazinyl)	-OCF ₃
20	BGR	-3-(4-chloropyridazinyl)	-Cl
	BGS	-3-(4-chloropyridazinyl)	-Br
	BGT	-3-(4-chloropyridazinyl)	-I
	BGU	-3-(4-chloropyridazinyl)	-n-butyl
	BGV	-3-(4-chloropyridazinyl)	-n-propyl
25	BGW	-3-(4-methylpyridazinyl)	-t-butyl
	BGX	-3-(4-methylpyridazinyl)	-iso-butyl
	BGY	-3-(4-methylpyridazinyl)	-sec-butyl
	BGZ	-3-(4-methylpyridazinyl)	-cyclohexyl
	BHA	-3-(4-methylpyridazinyl)	-t-butoxy
	BHB	-3-(4-methylpyridazinyl)	-isopropoxy
	BHC	-3-(4-methylpyridazinyl)	-CF ₃
	BHD	-3-(4-methylpyridazinyl)	-CH ₂ CF ₃
	BHE	-3-(4-methylpyridazinyl)	-OCF ₃

5	BHF	-3-(4-methylpyridazinyl)	-Cl
	BHG	-3-(4-methylpyridazinyl)	-Br
	BHH	-3-(4-methylpyridazinyl)	-I
	BHI	-3-(4-methylpyridazinyl)	-n-butyl
	BHJ	-3-(4-methylpyridazinyl)	-n-propyl
10	BHK	-3-(4-fluoropyridazinyl)	-t-butyl
	BHL	-3-(4-fluoropyridazinyl)	-iso-butyl
	BHM	-3-(4-fluoropyridazinyl)	-sec-butyl
	BHN	-3-(4-fluoropyridazinyl)	-cyclohexyl
	BHO	-3-(4-fluoropyridazinyl)	-t-butoxy
15	BHP	-3-(4-fluoropyridazinyl)	-isopropoxy
	BHQ	-3-(4-fluoropyridazinyl)	-CF ₃
	BHR	-3-(4-fluoropyridazinyl)	-CH ₂ CF ₃
	BHS	-3-(4-fluoropyridazinyl)	-OCF ₃
	BHT	-3-(4-fluoropyridazinyl)	-Cl
20	BHU	-3-(4-fluoropyridazinyl)	-Br
	BHV	-3-(4-fluoropyridazinyl)	-I
	BHW	-3-(4-fluoropyridazinyl)	-n-butyl
	BHX	-3-(4-fluoropyridazinyl)	-n-propyl
	BHY	-5-(4-chlorothiadiazolyl)	-t-butyl
25	BHZ	-5-(4-chlorothiadiazolyl)	-iso-butyl
	BIA	-5-(4-chlorothiadiazolyl)	-sec-butyl
	BIB	-5-(4-chlorothiadiazolyl)	-cyclohexyl
	BIC	-5-(4-chlorothiadiazolyl)	-t-butoxy
	BID	-5-(4-chlorothiadiazolyl)	-isopropoxy
	BIE	-5-(4-chlorothiadiazolyl)	-CF ₃
	BIF	-5-(4-chlorothiadiazolyl)	-CH ₂ CF ₃
	BIG	-5-(4-chlorothiadiazolyl)	-OCF ₃
	BIH	-5-(4-chlorothiadiazolyl)	-Cl

5	BII	-5-(4-chlorothiadiazolyl)	-Br
	BIJ	-5-(4-chlorothiadiazolyl)	-I
	BIK	-5-(4-chlorothiadiazolyl)	-n-butyl
	BIL	-5-(4-chlorothiadiazolyl)	-n-propyl
	BIM	-5-(4-methylthiadiazolyl)	-t-butyl
10	BIN	-5-(4-methylthiadiazolyl)	-iso-butyl
	BIO	-5-(4-methylthiadiazolyl)	-sec-butyl
	BIP	-5-(4-methylthiadiazolyl)	-cyclohexyl
	BIQ	-5-(4-methylthiadiazolyl)	-t-butoxy
	BIR	-5-(4-methylthiadiazolyl)	-isopropoxy
15	BIS	-5-(4-methylthiadiazolyl)	-CF ₃
	BIT	-5-(4-methylthiadiazolyl)	-CH ₂ CF ₃
	BIU	-5-(4-methylthiadiazolyl)	-OCF ₃
	BIV	-5-(4-methylthiadiazolyl)	-Cl
	BIW	-5-(4-methylthiadiazolyl)	-Br
20	BIX	-5-(4-methylthiadiazolyl)	-I
	BIY	-5-(4-methylthiadiazolyl)	-n-butyl
	BIZ	-5-(4-methylthiadiazolyl)	-n-propyl
	BJA	-5-(4-fluorothiadiazolyl)	-t-butyl
	BJB	-5-(4-fluorothiadiazolyl)	-iso-butyl
25	BJC	-5-(4-fluorothiadiazolyl)	-sec-butyl
	BJD	-5-(4-fluorothiadiazolyl)	-cyclohexyl
	BJE	-5-(4-fluorothiadiazolyl)	-t-butoxy
	BJF	-5-(4-fluorothiadiazolyl)	-isopropoxy
	BJG	-5-(4-fluorothiadiazolyl)	-CF ₃
	BJH	-5-(4-fluorothiadiazolyl)	-CH ₂ CF ₃
	BJI	-5-(4-fluorothiadiazolyl)	-OCF ₃
	BJJ	-5-(4-fluorothiadiazolyl)	-Cl
	BJK	-5-(4-fluorothiadiazolyl)	-Br

BJL	-5-(4-fluorothiadiazolyl)	-I
BJM	-5-(4-fluorothiadiazolyl)	-n-butyl
BJN	-5-(4-fluorothiadiazolyl)	-n-propyl

Table 4



IX

and pharmaceutically acceptable salts thereof, wherein:

Compound	Ar	R⁹
BJO (a and b)	-2-(3-chloropyridyl)	-t-butyl
BJP (a and b)	-2-(3-chloropyridyl)	-iso-butyl
BJQ (a and b)	-2-(3-chloropyridyl)	-sec-butyl
BJR (a and b)	-2-(3-chloropyridyl)	-cyclohexyl
BJS (a and b)	-2-(3-chloropyridyl)	-t-butoxy
BJT (a and b)	-2-(3-chloropyridyl)	-isopropoxy
BJU (a and b)	-2-(3-chloropyridyl)	-CF ₃
BJV (a and b)	-2-(3-chloropyridyl)	-CH ₂ CF ₃
BJW (a and b)	-2-(3-chloropyridyl)	-OCF ₃
BJX (a and b)	-2-(3-chloropyridyl)	-Cl
BJY (a and b)	-2-(3-chloropyridyl)	-Br
BJZ (a and b)	-2-(3-chloropyridyl)	-I
BKA (a and b)	-2-(3-chloropyridyl)	-n-butyl
BKB (a and b)	-2-(3-chloropyridyl)	-n-propyl
BKC (a and b)	-2-(3-fluoropyridyl)	-t-butyl

5	BKD (a and b)	-2-(3-fluoropyridyl)	-iso-butyl
	BKE (a and b)	-2-(3-fluoropyridyl)	-sec-butyl
	BKF (a and b)	-2-(3-fluoropyridyl)	-cyclohexyl
	BKG (a and b)	-2-(3-fluoropyridyl)	-t-butoxy
	BKH (a and b)	-2-(3-fluoropyridyl)	-isopropoxy
10	BKI (a and b)	-2-(3-fluoropyridyl)	-CF ₃
	BKJ (a and b)	-2-(3-fluoropyridyl)	-CH ₂ CF ₃
	BKK (a and b)	-2-(3-fluoropyridyl)	-OCF ₃
	BKL (a and b)	-2-(3-fluoropyridyl)	-Cl
	BKM (a and b)	-2-(3-fluoropyridyl)	-Br
15	BKN (a and b)	-2-(3-fluoropyridyl)	-I
	BKO (a and b)	-2-(3-fluoropyridyl)	-n-butyl
	BKP (a and b)	-2-(3-fluoropyridyl)	-n-propyl
	BKQ (a and b)	-2-(3-methylpyridyl)	-t-butyl
	BKR (a and b)	-2-(3-methylpyridyl)	-iso-butyl
20	BKS (a and b)	-2-(3-methylpyridyl)	-sec-butyl
	BKT (a and b)	-2-(3-methylpyridyl)	-cyclohexyl
	BKU (a and b)	-2-(3-methylpyridyl)	-t-butoxy
	BKV (a and b)	-2-(3-methylpyridyl)	-isopropoxy
	BKW (a and b)	-2-(3-methylpyridyl)	-CF ₃
25	BKX (a and b)	-2-(3-methylpyridyl)	-CH ₂ CF ₃
	BKY (a and b)	-2-(3-methylpyridyl)	-OCF ₃
	BKZ (a and b)	-2-(3-methylpyridyl)	-Cl
	BLA (a and b)	-2-(3-methylpyridyl)	-Br
	BLB (a and b)	-2-(3-methylpyridyl)	-I
	BLC (a and b)	-2-(3-methylpyridyl)	-n-butyl
	BLD (a and b)	-2-(3-methylpyridyl)	-n-propyl
	BLE (a and b)	-2(3-CF ₃ -pyridyl)	-t-butyl
	BLF (a and b)	-2-(3-CF ₃ -pyridyl)	-iso-butyl

	BLG (a and b)	-2-(3-CF ₃ -pyridyl)	-sec-butyl
	BLH (a and b)	-2-(3-CF ₃ -pyridyl)	-cyclohexyl
	BLI (a and b)	-2-(3-CF ₃ -pyridyl)	-t-butoxy
	BLJ (a and b)	-2-(3-CF ₃ -pyridyl)	-isopropoxy
5	BLK (a and b)	-2-(3-CF ₃ -pyridyl)	-CF ₃
	BLL (a and b)	-2-(3-CF ₃ -pyridyl)	-CH ₂ CF ₃
	BLM (a and b)	-2-(3-CF ₃ -pyridyl)	-OCF ₃
	BLN (a and b)	-2-(3-CF ₃ -pyridyl)	-Cl
	BLO (a and b)	-2-(3-CF ₃ -pyridyl)	-Br
10	BLP (a and b)	-2-(3-CF ₃ -pyridyl)	-I
	BLQ (a and b)	-2-(3-CF ₃ -pyridyl)	-n-butyl
	BLR (a and b)	-2-(3-CF ₃ -pyridyl)	-n-propyl
	BLS (a and b)	-2-(3-CHF ₂ -pyridyl)	-t-butyl
	BLT (a and b)	-2-(3-CHF ₂ -pyridyl)	-iso-butyl
15	BLU (a and b)	-2-(3-CHF ₂ -pyridyl)	-sec-butyl
	BLV (a and b)	-2-(3-CHF ₂ -pyridyl)	-cyclohexyl
	BLW (a and b)	-2-(3-CHF ₂ -pyridyl)	-t-butoxy
	BLX (a and b)	-2-(3-CHF ₂ -pyridyl)	-isopropoxy
	BLY (a and b)	-2-(3-CHF ₂ -pyridyl)	-CF ₃
20	BLZ (a and b)	-2-(3-CHF ₂ -pyridyl)	-CH ₂ CF ₃
	BMA (a and b)	-2-(3-CHF ₂ -pyridyl)	-OCF ₃
	BMB (a and b)	-2-(3-CHF ₂ -pyridyl)	-Cl
	BMC (a and b)	-2-(3-CHF ₂ -pyridyl)	-Br
	BMD (a and b)	-2-(3-CHF ₂ -pyridyl)	-I
25	BME (a and b)	-2-(3-CHF ₂ -pyridyl)	-n-butyl
	BMF (a and b)	-2-(3-CHF ₂ -pyridyl)	-n-propyl
	BMG (a and b)	-2-(3-hydroxypyridyl)	-t-butyl
	BMH (a and b)	-2-(3-hydroxypyridyl)	-iso-butyl
	BMI (a and b)	-2-(3-hydroxypyridyl)	-sec-butyl

5	BMJ (a and b)	-2-(3-hydroxypyridyl)	-cyclohexyl
	BMK (a and b)	-2-(3-hydroxypyridyl)	-t-butoxy
	BML (a and b)	-2-(3-hydroxypyridyl)	-isopropoxy
	BMM (a and b)	-2-(3-hydroxypyridyl)	-CF ₃
	BMN (a and b)	-2-(3-hydroxypyridyl)	-CH ₂ CF ₃
10	BMO (a and b)	-2-(3-hydroxypyridyl)	-OCF ₃
	BMP (a and b)	-2-(3-hydroxypyridyl)	-Cl
	BMQ (a and b)	-2-(3-hydroxypyridyl)	-Br
	BMR (a and b)	-2-(3-hydroxypyridyl)	-I
	BMS (a and b)	-2-(3-hydroxypyridyl)	-n-butyl
15	BMT (a and b)	-2-(3-hydroxypyridyl)	-n-propyl
	BMU (a and b)	-2-(3-nitropyridyl)	-t-butyl
	BMV (a and b)	-2-(3-nitropyridyl)	-iso-butyl
	BMW (a and b)	-2-(3-nitropyridyl)	-sec-butyl
	BMX (a and b)	-2-(3-nitropyridyl)	-cyclohexyl
20	BMY (a and b)	-2-(3-nitropyridyl)	-t-butoxy
	BMZ (a and b)	-2-(3-nitropyridyl)	-isopropoxy
	BNA (a and b)	-2-(3-nitropyridyl)	-CF ₃
	BNB (a and b)	-2-(3-nitropyridyl)	-CH ₂ CF ₃
	BNC (a and b)	-2-(3-nitropyridyl)	-OCF ₃
25	BND (a and b)	-2-(3-nitropyridyl)	-Cl
	BNE (a and b)	-2-(3-nitropyridyl)	-Br
	BNF (a and b)	-2-(3-nitropyridyl)	-I
	BNG (a and b)	-2-(3-nitropyridyl)	-n-butyl
	BNH (a and b)	-2-(3-nitropyridyl)	-n-propyl
	BNI (a and b)	-2-(3-cyanopyridyl)	-t-butyl
	BNJ (a and b)	-2-(3-cyanopyridyl)	-iso-butyl
	BNK (a and b)	-2-(3-cyanopyridyl)	-sec-butyl
	BNL (a and b)	-2-(3-cyanopyridyl)	-cyclohexyl

5	BNM (a and b)	-2-(3-cyanopyridyl)	-t-butoxy
	BNN (a and b)	-2-(3-cyanopyridyl)	-isopropoxy
	BNO (a and b)	-2-(3-cyanopyridyl)	-CF ₃
	BNP (a and b)	-2-(3-cyanopyridyl)	-CH ₂ CF ₃
	BNQ (a and b)	-2-(3-cyanopyridyl)	-OCF ₃
10	BNR (a and b)	-2-(3-cyanopyridyl)	-Cl
	BNS (a and b)	-2-(3-cyanopyridyl)	-Br
	BNT (a and b)	-2-(3-cyanopyridyl)	-I
	BNU (a and b)	-2-(3-cyanopyridyl)	-n-butyl
	BNV (a and b)	-2-(3-cyanopyridyl)	-n-propyl
15	BNW (a and b)	-2-(3-bromopyridyl)	-t-butyl
	BNX (a and b)	-2-(3-bromopyridyl)	-iso-butyl
	BNY (a and b)	-2-(3-bromopyridyl)	-sec-butyl
	BNZ (a and b)	-2-(3-bromopyridyl)	-cyclohexyl
	BOA (a and b)	-2-(3-bromopyridyl)	-t-butoxy
20	BOB (a and b)	-2-(3-bromopyridyl)	-isopropoxy
	BOC (a and b)	-2-(3-bromopyridyl)	-CF ₃
	BOD (a and b)	-2-(3-bromopyridyl)	-CH ₂ CF ₃
	BOE (a and b)	-2-(3-bromopyridyl)	-OCF ₃
	BOF (a and b)	-2-(3-bromopyridyl)	-Cl
25	BOG (a and b)	-2-(3-bromopyridyl)	-Br
	BOH (a and b)	-2-(3-bromopyridyl)	-I
	BOI (a and b)	-2-(3-bromopyridyl)	-n-butyl
	BOJ (a and b)	-2-(3-bromopyridyl)	-n-propyl
	BOK (a and b)	-2-(3-iodopyridyl)	-t-butyl
	BOL (a and b)	-2-(3-iodopyridyl)	-iso-butyl
	BOM (a and b)	-2-(3-iodopyridyl)	-sec-butyl
	BON (a and b)	-2-(3-iodopyridyl)	-cyclohexyl
	BOO (a and b)	-2-(3-iodopyridyl)	-t-butoxy

5	BOP (a and b)	-2-(3-iodopyridyl)	-isopropoxy
	BOQ (a and b)	-2-(3-iodopyridyl)	-CF ₃
	BOR (a and b)	-2-(3-iodopyridyl)	-CH ₂ CF ₃
	BOS (a and b)	-2-(3-iodopyridyl)	-OCF ₃
	BOT (a and b)	-2-(3-iodopyridyl)	-Cl
10	BOU (a and b)	-2-(3-iodopyridyl)	-Br
	BOV (a and b)	-2-(3-iodopyridyl)	-I
	BOW (a and b)	-2-(3-iodopyridyl)	-n-butyl
	BOX (a and b)	-2-(3-iodopyridyl)	-n-propyl
	BOY (a and b)	-4-(5-chloropyrimidinyl)	-t-butyl
15	BOZ (a and b)	-4-(5-chloropyrimidinyl)	-iso-butyl
	BPA (a and b)	-4-(5-chloropyrimidinyl)	-sec-butyl
	BPB (a and b)	-4-(5-chloropyrimidinyl)	-cyclohexyl
	BPC (a and b)	-4-(5-chloropyrimidinyl)	-t-butoxy
	BPD (a and b)	-4-(5-chloropyrimidinyl)	-isopropoxy
20	BPE (a and b)	-4-(5-chloropyrimidinyl)	-CF ₃
	BPF (a and b)	-4-(5-chloropyrimidinyl)	-CH ₂ CF ₃
	BPG (a and b)	-4-(5-chloropyrimidinyl)	-OCF ₃
	BPH (a and b)	-4-(5-chloropyrimidinyl)	-Cl
	BPI (a and b)	-4-(5-chloropyrimidinyl)	-Br
25	BPJ (a and b)	-4-(5-chloropyrimidinyl)	-I
	BPK (a and b)	-4-(5-chloropyrimidinyl)	-n-butyl
	BPL (a and b)	-4-(5-chloropyrimidinyl)	-n-propyl
	BPM (a and b)	-4-(5-methylpyrimidinyl)	-t-butyl
	BPN (a and b)	-4-(5-methylpyrimidinyl)	-iso-butyl
	BPO (a and b)	-4-(5-methylpyrimidinyl)	-sec-butyl
	BPP (a and b)	-4-(5-methylpyrimidinyl)	-cyclohexyl
	BPQ (a and b)	-4-(5-methylpyrimidinyl)	-t-butoxy
	BPR (a and b)	-4-(5-methylpyrimidinyl)	-isopropoxy

5	BPS (a and b)	-4-(5-methylpyrimidinyl)	-CF ₃
	BPT (a and b)	-4-(5-methylpyrimidinyl)	-CH ₂ CF ₃
	BPU (a and b)	-4-(5-methylpyrimidinyl)	-OCF ₃
	BPV (a and b)	-4-(5-methylpyrimidinyl)	-Cl
	BPW (a and b)	-4-(5-methylpyrimidinyl)	-Br
10	BPX (a and b)	-4-(5-methylpyrimidinyl)	-I
	BPY (a and b)	-4-(5-methylpyrimidinyl)	-n-butyl
	BPZ (a and b)	-4-(5-methylpyrimidinyl)	-n-propyl
	BQA (a and b)	-4-(5-fluoropyrimidinyl)	-t-butyl
	BQB (a and b)	-4-(5-fluoropyrimidinyl)	-iso-butyl
15	BQC (a and b)	-4-(5-fluoropyrimidinyl)	-sec-butyl
	BQD (a and b)	-4-(5-fluoropyrimidinyl)	-cyclohexyl
	BQE (a and b)	-4-(5-fluoropyrimidinyl)	-t-butoxy
	BQF (a and b)	-4-(5-fluoropyrimidinyl)	-isopropoxy
	BQG (a and b)	-4-(5-fluoropyrimidinyl)	-CF ₃
20	BQH (a and b)	-4-(5-fluoropyrimidinyl)	-CH ₂ CF ₃
	BQI (a and b)	-4-(5-fluoropyrimidinyl)	-OCF ₃
	BQJ (a and b)	-4-(5-fluoropyrimidinyl)	-Cl
	BQK (a and b)	-4-(5-fluoropyrimidinyl)	-Br
	BQL (a and b)	-4-(5-fluoropyrimidinyl)	-I
25	BQM (a and b)	-4-(5-fluoropyrimidinyl)	-n-butyl
	BQN (a and b)	-4-(5-fluoropyrimidinyl)	-n-propyl
	BQO (a and b)	-2-(3-chloropyrazinyl)	-t-butyl
	BQP (a and b)	-2-(3-chloropyrazinyl)	-iso-butyl
	BQQ (a and b)	-2-(3-chloropyrazinyl)	-sec-butyl
	BQR (a and b)	-2-(3-chloropyrazinyl)	-cyclohexyl
	BQS (a and b)	-2-(3-chloropyrazinyl)	-t-butoxy
	BQT (a and b)	-2-(3-chloropyrazinyl)	-isopropoxy
	BQU (a and b)	-2-(3-chloropyrazinyl)	-CF ₃

5	BQV (a and b)	-2-(3-chloropyrazinyl)	-CH ₂ CF ₃
	BQW (a and b)	-2-(3-chloropyrazinyl)	-OCF ₃
	BQX (a and b)	-2-(3-chloropyrazinyl)	-Cl
	BQY (a and b)	-2-(3-chloropyrazinyl)	-Br
	BQZ (a and b)	-2-(3-chloropyrazinyl)	-I
10	BRA (a and b)	-2-(3-chloropyrazinyl)	-n-butyl
	BRB (a and b)	-2-(3-chloropyrazinyl)	-n-propyl
	BRC (a and b)	-2-(3-methylpyrazinyl)	-t-butyl
	BRD (a and b)	-2-(3-methylpyrazinyl)	-iso-butyl
	BRE (a and b)	-2-(3-methylpyrazinyl)	-sec-butyl
15	BRF (a and b)	-2-(3-methylpyrazinyl)	-cyclohexyl
	BRG (a and b)	-2-(3-methylpyrazinyl)	-t-butoxy
	BRH (a and b)	-2-(3-methylpyrazinyl)	-isopropoxy
	BRI (a and b)	-2-(3-methylpyrazinyl)	-CF ₃
	BRJ (a and b)	-2-(3-methylpyrazinyl)	-CH ₂ CF ₃
20	BRK (a and b)	-2-(3-methylpyrazinyl)	-OCF ₃
	BRL (a and b)	-2-(3-methylpyrazinyl)	-Cl
	BRM (a and b)	-2-(3-methylpyrazinyl)	-Br
	BRN (a and b)	-2-(3-methylpyrazinyl)	-I
	BRO (a and b)	-2-(3-methylpyrazinyl)	-n-butyl
25	BRP (a and b)	-2-(3-methylpyrazinyl)	-n-propyl
	BRQ (a and b)	-2-(3-fluoropyrazinyl)	-t-butyl
	BRR (a and b)	-2-(3-fluoropyrazinyl)	-iso-butyl
	BRS (a and b)	-2-(3-fluoropyrazinyl)	-sec-butyl
	BRT (a and b)	-2-(3-fluoropyrazinyl)	-cyclohexyl
	BRU (a and b)	-2-(3-fluoropyrazinyl)	-t-butoxy
	BRV (a and b)	-2-(3-fluoropyrazinyl)	-isopropoxy
	BRW (a and b)	-2-(3-fluoropyrazinyl)	-CF ₃
	BRX (a and b)	-2-(3-fluoropyrazinyl)	-CH ₂ CF ₃

5	BRY (a and b)	-2-(3-fluoropyrazinyl)	-OCF ₃
	BRZ (a and b)	-2-(3-fluoropyrazinyl)	-Cl
	BSA (a and b)	-2-(3-fluoropyrazinyl)	-Br
	BSB (a and b)	-2-(3-fluoropyrazinyl)	-I
	BSC (a and b)	-2-(3-fluoropyrazinyl)	-n-butyl
10	BSD (a and b)	-2-(3-fluoropyrazinyl)	-n-propyl
	BSE (a and b)	-3-(4-chloropyridazinyl)	-t-butyl
	BSF (a and b)	-3-(4-chloropyridazinyl)	-iso-butyl
	BSG (a and b)	-3-(4-chloropyridazinyl)	-sec-butyl
	BSH (a and b)	-3-(4-chloropyridazinyl)	-cyclohexyl
15	BSI (a and b)	-3-(4-chloropyridazinyl)	-t-butoxy
	BSJ (a and b)	-3-(4-chloropyridazinyl)	-isopropoxy
	BSK (a and b)	-3-(4-chloropyridazinyl)	-CF ₃
	BSL (a and b)	-3-(4-chloropyridazinyl)	-CH ₂ CF ₃
	BSM (a and b)	-3-(4-chloropyridazinyl)	-OCF ₃
20	BSN (a and b)	-3-(4-chloropyridazinyl)	-Cl
	BSO (a and b)	-3-(4-chloropyridazinyl)	-Br
	BSP (a and b)	-3-(4-chloropyridazinyl)	-I
	BSQ (a and b)	-3-(4-chloropyridazinyl)	-n-butyl
	BSR (a and b)	-3-(4-chloropyridazinyl)	-n-propyl
25	BSS (a and b)	-3-(4-methylpyridazinyl)	-t-butyl
	BST (a and b)	-3-(4-methylpyridazinyl)	-iso-butyl
	BSU (a and b)	-3-(4-methylpyridazinyl)	-sec-butyl
	BSV (a and b)	-3-(4-methylpyridazinyl)	-cyclohexyl
	BSW (a and b)	-3-(4-methylpyridazinyl)	-t-butoxy
	BSX (a and b)	-3-(4-methylpyridazinyl)	-isopropoxy
	BSY (a and b)	-3-(4-methylpyridazinyl)	-CF ₃
	BSZ (a and b)	-3-(4-methylpyridazinyl)	-CH ₂ CF ₃
	BTA (a and b)	-3-(4-methylpyridazinyl)	-OCF ₃

5	BTB (a and b)	-3-(4-methylpyridazinyl)	-Cl
	BTC (a and b)	-3-(4-methylpyridazinyl)	-Br
	BTD (a and b)	-3-(4-methylpyridazinyl)	-I
	BTE (a and b)	-3-(4-methylpyridazinyl)	-n-butyl
	BTF (a and b)	-3-(4-methylpyridazinyl)	-n-propyl
10	BTG (a and b)	-3-(4-fluoropyridazinyl)	-t-butyl
	BTH (a and b)	-3-(4-fluoropyridazinyl)	-iso-butyl
	BTI (a and b)	-3-(4-fluoropyridazinyl)	-sec-butyl
	BTJ (a and b)	-3-(4-fluoropyridazinyl)	-cyclohexyl
	BTK (a and b)	-3-(4-fluoropyridazinyl)	-t-butoxy
15	BTL (a and b)	-3-(4-fluoropyridazinyl)	-isopropoxy
	BTM (a and b)	-3-(4-fluoropyridazinyl)	-CF ₃
	BTN (a and b)	-3-(4-fluoropyridazinyl)	-CH ₂ CF ₃
	BTO (a and b)	-3-(4-fluoropyridazinyl)	-OCF ₃
	BTP (a and b)	-3-(4-fluoropyridazinyl)	-Cl
20	BTQ (a and b)	-3-(4-fluoropyridazinyl)	-Br
	BTR (a and b)	-3-(4-fluoropyridazinyl)	-I
	BTS (a and b)	-3-(4-fluoropyridazinyl)	-n-butyl
	BTT (a and b)	-3-(4-fluoropyridazinyl)	-n-propyl
	BTU (a and b)	-5-(4-chlorothiadiazo- lyl)	-t-butyl
25	BTV (a and b)	-5-(4-chlorothiadiazo- lyl)	-iso-butyl
	BTW (a and b)	-5-(4-chlorothiadiazo- lyl)	-sec-butyl
	BTX (a and b)	-5-(4-chlorothiadiazo- lyl)	-cyclohexyl
	BTY (a and b)	-5-(4-chlorothiadiazo- lyl)	-t-butoxy
	BTZ (a and b)	-5-(4-chlorothiadiazo- lyl)	-isopropoxy
	BUA (a and b)	-5-(4-chlorothiadiazo- lyl)	-CF ₃
	BUB (a and b)	-5-(4-chlorothiadiazo- lyl)	-CH ₂ CF ₃
	BUC (a and b)	-5-(4-chlorothiadiazo- lyl)	-OCF ₃
	BUD (a and b)	-5-(4-chlorothiadiazo- lyl)	-Cl

5	BUE (a and b)	-5-(4-chlorothiadiazolyl)	-Br
	BUF (a and b)	-5-(4-chlorothiadiazolyl)	-I
	BUG (a and b)	-5-(4-chlorothiadiazolyl)	-n-butyl
	BUH (a and b)	-5-(4-chlorothiadiazolyl)	-n-propyl
	BUI (a and b)	-5-(4-methylthiadiazolyl)	-t-butyl
10	BUJ (a and b)	-5-(4-methylthiadiazolyl)	-iso-butyl
	BUK (a and b)	-5-(4-methylthiadiazolyl)	-sec-butyl
	BUL (a and b)	-5-(4-methylthiadiazolyl)	-cyclohexyl
	BUM (a and b)	-5-(4-methylthiadiazolyl)	-t-butoxy
	BUN (a and b)	-5-(4-methylthiadiazolyl)	-isopropoxy
15	BUO (a and b)	-5-(4-methylthiadiazolyl)	-CF ₃
	BUP (a and b)	-5-(4-methylthiadiazolyl)	-CH ₂ CF ₃
	BUQ (a and b)	-5-(4-methylthiadiazolyl)	-OCF ₃
	BUR (a and b)	-5-(4-methylthiadiazolyl)	-Cl
	BUS (a and b)	-5-(4-methylthiadiazolyl)	-Br
20	BUT (a and b)	-5-(4-methylthiadiazolyl)	-I
	BUU (a and b)	-5-(4-methylthiadiazolyl)	-n-butyl
	BUV (a and b)	-5-(4-methylthiadiazolyl)	-n-propyl
	BUW (a and b)	-5-(4-fluorothiadiazolyl)	-t-butyl
	BUX (a and b)	-5-(4-fluorothiadiazolyl)	-iso-butyl
25	BUY (a and b)	-5-(4-fluorothiadiazolyl)	-sec-butyl
	BUZ (a and b)	-5-(4-fluorothiadiazolyl)	-cyclohexyl
	BVA (a and b)	-5-(4-fluorothiadiazolyl)	-t-butoxy
	BVB (a and b)	-5-(4-fluorothiadiazolyl)	-isopropoxy
	BVC (a and b)	-5-(4-fluorothiadiazolyl)	-CF ₃
	BVD (a and b)	-5-(4-fluorothiadiazolyl)	-CH ₂ CF ₃
	BVE (a and b)	-5-(4-fluorothiadiazolyl)	-OCF ₃
	BVF (a and b)	-5-(4-fluorothiadiazolyl)	-Cl
	BVG (a and b)	-5-(4-fluorothiadiazolyl)	-Br

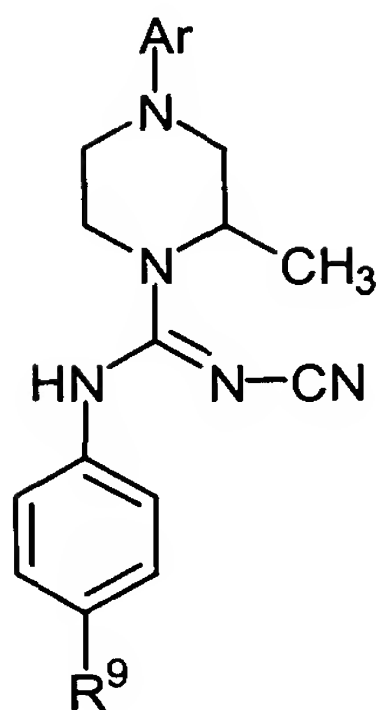
BVH (a and b)	-5-(4-fluorothiadiazolyl)	-I
BVI (a and b)	-5-(4-fluorothiadiazolyl)	-n-butyl
BVJ (a and b)	-5-(4-fluorothiadiazolyl)	-n-propyl

wherein “a” means that the carbon atom of the piperazino group to which the
5 methyl group is attached is in the R configuration and “b” means that the carbon of the
piperazino group to which the methyl group is attached is in the S configuration

10

15

Table 5



X

and pharmaceutically acceptable salts thereof, wherein:

	<u>Compound</u>	<u>Ar</u>	<u>R⁹</u>
15	BVK (a and b)	-2-(3-chloropyridyl)	-t-butyl
	BVL (a and b)	-2-(3-chloropyridyl)	-iso-butyl
	BVM (a and b)	-2-(3-chloropyridyl)	-sec-butyl
	BVN (a and b)	-2-(3-chloropyridyl)	-cyclohexyl
	BVO (a and b)	-2-(3-chloropyridyl)	-t-butoxy
20	BVP (a and b)	-2-(3-chloropyridyl)	-isopropoxy
	BVQ (a and b)	-2-(3-chloropyridyl)	-CF ₃
	BVR (a and b)	-2-(3-chloropyridyl)	-CH ₂ CF ₃
	BVS (a and b)	-2-(3-chloropyridyl)	-OCF ₃
	BVT (a and b)	-2-(3-chloropyridyl)	-Cl
25	BVU (a and b)	-2-(3-chloropyridyl)	-Br
	BVV (a and b)	-2-(3-chloropyridyl)	-I
	BVW (a and b)	-2-(3-chloropyridyl)	-n-butyl
	BVX (a and b)	-2-(3-chloropyridyl)	-n-propyl
	BVY (a and b)	-2-(3-fluoropyridyl)	-t-butyl
30	BVZ (a and b)	-2-(3-fluoropyridyl)	-iso-butyl

5	BWA (a and b)	-2-(3-fluoropyridyl)	-sec-butyl
	BWB (a and b)	-2-(3-fluoropyridyl)	-cyclohexyl
	BWC (a and b)	-2-(3-fluoropyridyl)	-t-butoxy
	BWD (a and b)	-2-(3-fluoropyridyl)	-isopropoxy
	BWE (a and b)	-2-(3-fluoropyridyl)	-CF ₃
10	BWF (a and b)	-2-(3-fluoropyridyl)	-CH ₂ CF ₃
	BWG (a and b)	-2-(3-fluoropyridyl)	-OCF ₃
	BWH (a and b)	-2-(3-fluoropyridyl)	-Cl
	BWI (a and b)	-2-(3-fluoropyridyl)	-Br
	BWJ (a and b)	-2-(3-fluoropyridyl)	-I
15	BWK (a and b)	-2-(3-fluoropyridyl)	-n-butyl
	BWL (a and b)	-2-(3-fluoropyridyl)	-n-propyl
	BWM (a and b)	-2-(3-methylpyridyl)	-t-butyl
	BWN (a and b)	-2-(3-methylpyridyl)	-iso-butyl
	BWO (a and b)	-2-(3-methylpyridyl)	-sec-butyl
20	BWP (a and b)	-2-(3-methylpyridyl)	-cyclohexyl
	BWQ (a and b)	-2-(3-methylpyridyl)	-t-butoxy
	BWR (a and b)	-2-(3-methylpyridyl)	-isopropoxy
	BWS (a and b)	-2-(3-methylpyridyl)	-CF ₃
	BWT (a and b)	-2-(3-methylpyridyl)	-CH ₂ CF ₃
25	BWU (a and b)	-2-(3-methylpyridyl)	-OCF ₃
	BWV (a and b)	-2-(3-methylpyridyl)	-Cl
	BWW (a and b)	-2-(3-methylpyridyl)	-Br
	BWX (a and b)	-2-(3-methylpyridyl)	-I
	BWY (a and b)	-2-(3-methylpyridyl)	-n-butyl
	BWZ (a and b)	-2-(3-methylpyridyl)	-n-propyl
	BXA (a and b)	-2-(3-CF ₃ -pyridyl)	-t-butyl
	BXB (a and b)	-2-(3-CF ₃ -pyridyl)	-iso-butyl
	BXC (a and b)	-2-(3-CF ₃ -pyridyl)	-sec-butyl

5	BXD (a and b)	-2-(3-CF ₃ -pyridyl)	-cyclohexyl
	BXE (a and b)	-2-(3-CF ₃ -pyridyl)	-t-butoxy
	BXF (a and b)	-2-(3-CF ₃ -pyridyl)	-isopropoxy
	BXG (a and b)	-2-(3-CF ₃ -pyridyl)	-CF ₃
	BXH (a and b)	-2-(3-CF ₃ -pyridyl)	-CH ₂ CF ₃
10	BXI (a and b)	-2-(3-CF ₃ -pyridyl)	-OCF ₃
	BXJ (a and b)	-2-(3-CF ₃ -pyridyl)	-Cl
	BXK (a and b)	-2-(3-CF ₃ -pyridyl)	-Br
	BXL (a and b)	-2-(3-CF ₃ -pyridyl)	-I
	BXM (a and b)	-2-(3-CF ₃ -pyridyl)	-n-butyl
15	BXN (a and b)	-2-(3-CF ₃ -pyridyl)	-n-propyl
	BXO (a and b)	-2-(3-CHF ₂ -pyridyl)	-t-butyl
	BXP (a and b)	-2-(3-CHF ₂ -pyridyl)	-iso-butyl
	BXQ (a and b)	-2-(3-CHF ₂ -pyridyl)	-sec-butyl
	BXR (a and b)	-2-(3-CHF ₂ -pyridyl)	-cyclohexyl
20	BXS (a and b)	-2-(3-CHF ₂ -pyridyl)	-t-butoxy
	BXT (a and b)	-2-(3-CHF ₂ -pyridyl)	-isopropoxy
	BXU (a and b)	-2-(3-CHF ₂ -pyridyl)	-CF ₃
	BXV (a and b)	-2-(3-CHF ₂ -pyridyl)	-CH ₂ CF ₃
	BXW (a and b)	-2-(3-CHF ₂ -pyridyl)	-OCF ₃
25	BXX (a and b)	-2-(3-CHF ₂ -pyridyl)	-Cl
	BXY (a and b)	-2-(3-CHF ₂ -pyridyl)	-Br
	BXZ (a and b)	-2-(3-CHF ₂ -pyridyl)	-I
	BYA (a and b)	-2-(3-CHF ₂ -pyridyl)	-n-butyl
	BYB (a and b)	-2-(3-CHF ₂ -pyridyl)	-n-propyl
	BYC (a and b)	-2-(3-hydroxypyridyl)	-t-butyl
	BYD (a and b)	-2-(3-hydroxypyridyl)	-iso-butyl
	BYE (a and b)	-2-(3-hydroxypyridyl)	-sec-butyl
	BYF (a and b)	-2-(3-hydroxypyridyl)	-cyclohexyl

5	BYG (a and b)	-2-(3-hydroxypyridyl)	-t-butoxy
	BYH (a and b)	-2-(3-hydroxypyridyl)	-isopropoxy
	BYI (a and b)	-2-(3-hydroxypyridyl)	-CF ₃
	BYJ (a and b)	-2-(3-hydroxypyridyl)	-CH ₂ CF ₃
	BYK (a and b)	-2-(3-hydroxypyridyl)	-OCF ₃
10	BYL (a and b)	-2-(3-hydroxypyridyl)	-Cl
	BYM (a and b)	-2-(3-hydroxypyridyl)	-Br
	BYN (a and b)	-2-(3-hydroxypyridyl)	-I
	BYO (a and b)	-2-(3-hydroxypyridyl)	-n-butyl
	BYP (a and b)	-2-(3-hydroxypyridyl)	-n-propyl
15	BYQ (a and b)	-2-(3-nitropyridyl)	-t-butyl
	BYR (a and b)	-2-(3-nitropyridyl)	-iso-butyl
	BYS (a and b)	-2-(3-nitropyridyl)	-sec-butyl
	BYT (a and b)	-2-(3-nitropyridyl)	-cyclohexyl
	BYU (a and b)	-2-(3-nitropyridyl)	-t-butoxy
20	BYV (a and b)	-2-(3-nitropyridyl)	-isopropoxy
	BYW (a and b)	-2-(3-nitropyridyl)	-CF ₃
	BYX (a and b)	-2-(3-nitropyridyl)	-CH ₂ CF ₃
	BYY (a and b)	-2-(3-nitropyridyl)	-OCF ₃
	BYZ (a and b)	-2-(3-nitropyridyl)	-Cl
25	BZA (a and b)	-2-(3-nitropyridyl)	-Br
	BZB (a and b)	-2-(3-nitropyridyl)	-I
	BZC (a and b)	-2-(3-nitropyridyl)	-n-butyl
	BZD (a and b)	-2-(3-nitropyridyl)	-n-propyl
	BZE (a and b)	-2-(3-cyanopyridyl)	-t-butyl
	BZF (a and b)	-2-(3-cyanopyridyl)	-iso-butyl
	BZG (a and b)	-2-(3-cyanopyridyl)	-sec-butyl
	BZH (a and b)	-2-(3-cyanopyridyl)	-cyclohexyl
	BZI (a and b)	-2-(3-cyanopyridyl)	-t-butoxy

5	BZJ (a and b)	-2-(3-cyanopyridyl)	-isopropoxy
	BZK (a and b)	-2-(3-cyanopyridyl)	-CF ₃
	BZL (a and b)	-2-(3-cyanopyridyl)	-CH ₂ CF ₃
	BZM (a and b)	-2-(3-cyanopyridyl)	-OCF ₃
	BZN (a and b)	-2-(3-cyanopyridyl)	-Cl
10	BZO (a and b)	-2-(3-cyanopyridyl)	-Br
	BZP (a and b)	-2-(3-cyanopyridyl)	-I
	BZQ (a and b)	-2-(3-cyanopyridyl)	-n-butyl
	BZR (a and b)	-2-(3-cyanopyridyl)	-n-propyl
	BZS (a and b)	-2-(3-bromopyridyl)	-t-butyl
15	BZT (a and b)	-2-(3-bromopyridyl)	-iso-butyl
	BZU (a and b)	-2-(3-bromopyridyl)	-sec-butyl
	BZV (a and b)	-2-(3-bromopyridyl)	-cyclohexyl
	BZW (a and b)	-2-(3-bromopyridyl)	-t-butoxy
	BZX (a and b)	-2-(3-bromopyridyl)	-isopropoxy
20	BZY (a and b)	-2-(3-bromopyridyl)	-CF ₃
	BZZ (a and b)	-2-(3-bromopyridyl)	-CH ₂ CF ₃
	CAA (a and b)	-2-(3-bromopyridyl)	-OCF ₃
	CAB (a and b)	-2-(3-bromopyridyl)	-Cl
	CAC (a and b)	-2-(3-bromopyridyl)	-Br
25	CAD (a and b)	-2-(3-bromopyridyl)	-I
	CAE (a and b)	-2-(3-bromopyridyl)	-n-butyl
	CAF (a and b)	-2-(3-bromopyridyl)	-n-propyl
	CAG (a and b)	-2-(3-iodopyridyl)	-t-butyl
	CAH (a and b)	-2-(3-iodopyridyl)	-iso-butyl
	CAI (a and b)	-2-(3-iodopyridyl)	-sec-butyl
	CAJ (a and b)	-2-(3-iodopyridyl)	-cyclohexyl
	CAK (a and b)	-2-(3-iodopyridyl)	-t-butoxy
	CAL (a and b)	-2-(3-iodopyridyl)	-isopropoxy

5	CAM (a and b)	-2-(3-iodopyridyl)	-CF ₃
	CAN (a and b)	-2-(3-iodopyridyl)	-CH ₂ CF ₃
	CAO (a and b)	-2-(3-iodopyridyl)	-OCF ₃
	CAP (a and b)	-2-(3-iodopyridyl)	-Cl
	CAQ (a and b)	-2-(3-iodopyridyl)	-Br
10	CAR (a and b)	-2-(3-iodopyridyl)	-I
	CAS (a and b)	-2-(3-iodopyridyl)	-n-butyl
	CAT (a and b)	-2-(3-iodopyridyl)	-n-propyl
	CAU (a and b)	-4-(5-chloropyrimidinyl)	-t-butyl
	CAV (a and b)	-4-(5-chloropyrimidinyl)	-iso-butyl
15	CAW (a and b)	-4-(5-chloropyrimidinyl)	-sec-butyl
	CAX (a and b)	-4-(5-chloropyrimidinyl)	-cyclohexyl
	CAY (a and b)	-4-(5-chloropyrimidinyl)	-t-butoxy
	CAZ (a and b)	-4-(5-chloropyrimidinyl)	-isopropoxy
	CBA (a and b)	-4-(5-chloropyrimidinyl)	-CF ₃
20	CBB (a and b)	-4-(5-chloropyrimidinyl)	-CH ₂ CF ₃
	CBC (a and b)	-4-(5-chloropyrimidinyl)	-OCF ₃
	CBD (a and b)	-4-(5-chloropyrimidinyl)	-Cl
	CBE (a and b)	-4-(5-chloropyrimidinyl)	-Br
	CBF (a and b)	-4-(5-chloropyrimidinyl)	-I
25	CBG (a and b)	-4-(5-chloropyrimidinyl)	-n-butyl
	CBH (a and b)	-4-(5-chloropyrimidinyl)	-n-propyl
	CBI (a and b)	-4-(5-methylpyrimidinyl)	-t-butyl
	CBJ (a and b)	-4-(5-methylpyrimidinyl)	-iso-butyl
	CBK (a and b)	-4-(5-methylpyrimidinyl)	-sec-butyl
	CBL (a and b)	-4-(5-methylpyrimidinyl)	-cyclohexyl
	CBM (a and b)	-4-(5-methylpyrimidinyl)	-t-butoxy
	CBN (a and b)	-4-(5-methylpyrimidinyl)	-isopropoxy
	CBO (a and b)	-4-(5-methylpyrimidinyl)	-CF ₃

5	CBP (a and b)	-4-(5-methylpyrimidinyl)	-CH ₂ CF ₃
	CBQ (a and b)	-4-(5-methylpyrimidinyl)	-OCF ₃
	CBR (a and b)	-4-(5-methylpyrimidinyl)	-Cl
	CBS (a and b)	-4-(5-methylpyrimidinyl)	-Br
	CBT (a and b)	-4-(5-methylpyrimidinyl)	-I
10	CBU (a and b)	-4-(5-methylpyrimidinyl)	-n-butyl
	CBV (a and b)	-4-(5-methylpyrimidinyl)	-n-propyl
	CBW (a and b)	-4-(5-fluoropyrimidinyl)	-t-butyl
	CBX (a and b)	-4-(5-fluoropyrimidinyl)	-iso-butyl
	CBY (a and b)	-4-(5-fluoropyrimidinyl)	-sec-butyl
15	CBZ (a and b)	-4-(5-fluoropyrimidinyl)	-cyclohexyl
	CCA (a and b)	-4-(5-fluoropyrimidinyl)	-t-butoxy
	CCB (a and b)	-4-(5-fluoropyrimidinyl)	-isopropoxy
	CCC (a and b)	-4-(5-fluoropyrimidinyl)	-CF ₃
	CCD (a and b)	-4-(5-fluoropyrimidinyl)	-CH ₂ CF ₃
20	CCE (a and b)	-4-(5-fluoropyrimidinyl)	-OCF ₃
	CCF (a and b)	-4-(5-fluoropyrimidinyl)	-Cl
	CCG (a and b)	-4-(5-fluoropyrimidinyl)	-Br
	CCH (a and b)	-4-(5-fluoropyrimidinyl)	-I
	CCI (a and b)	-4-(5-fluoropyrimidinyl)	-n-butyl
25	CCJ (a and b)	-4-(5-fluoropyrimidinyl)	-n-propyl
	CCK (a and b)	-2-(3-chloropyrazinyl)	-t-butyl
	CCL (a and b)	-2-(3-chloropyrazinyl)	-iso-butyl
	CCM (a and b)	-2-(3-chloropyrazinyl)	-sec-butyl
	CCN (a and b)	-2-(3-chloropyrazinyl)	-cyclohexyl
	CCO (a and b)	-2-(3-chloropyrazinyl)	-t-butoxy
	CCP (a and b)	-2-(3-chloropyrazinyl)	-isopropoxy
	CCQ (a and b)	-2-(3-chloropyrazinyl)	-CF ₃
	CCR (a and b)	-2-(3-chloropyrazinyl)	-CH ₂ CF ₃

5	CCS (a and b)	-2-(3-chloropyrazinyl)	-OCF ₃
	CCT (a and b)	-2-(3-chloropyrazinyl)	-Cl
	CCU (a and b)	-2-(3-chloropyrazinyl)	-Br
	CCV (a and b)	-2-(3-chloropyrazinyl)	-I
	CCW (a and b)	-2-(3-chloropyrazinyl)	-n-butyl
10	CCX (a and b)	-2-(3-chloropyrazinyl)	-n-propyl
	CCY (a and b)	-2-(3-methylpyrazinyl)	-t-butyl
	CCZ (a and b)	-2-(3-methylpyrazinyl)	-iso-butyl
	CDA (a and b)	-2-(3-methylpyrazinyl)	-sec-butyl
	CDB (a and b)	-2-(3-methylpyrazinyl)	-cyclohexyl
15	CDC (a and b)	-2-(3-methylpyrazinyl)	-t-butoxy
	CDD (a and b)	-2-(3-methylpyrazinyl)	-isopropoxy
	CDE (a and b)	-2-(3-methylpyrazinyl)	-CF ₃
	CDF (a and b)	-2-(3-methylpyrazinyl)	-CH ₂ CF ₃
	CDG (a and b)	-2-(3-methylpyrazinyl)	-OCF ₃
20	CDH (a and b)	-2-(3-methylpyrazinyl)	-Cl
	CDI (a and b)	-2-(3-methylpyrazinyl)	-Br
	CDJ (a and b)	-2-(3-methylpyrazinyl)	-I
	CDK (a and b)	-2-(3-methylpyrazinyl)	-n-butyl
	CDL (a and b)	-2-(3-methylpyrazinyl)	-n-propyl
25	CDM (a and b)	-2-(3-fluoropyrazinyl)	-t-butyl
	CDN (a and b)	-2-(3-fluoropyrazinyl)	-iso-butyl
	CDO (a and b)	-2-(3-fluoropyrazinyl)	-sec-butyl
	CDP (a and b)	-2-(3-fluoropyrazinyl)	-cyclohexyl
	CDQ (a and b)	-2-(3-fluoropyrazinyl)	-t-butoxy
	CDR (a and b)	-2-(3-fluoropyrazinyl)	-isopropoxy
	CDS (a and b)	-2-(3-fluoropyrazinyl)	-CF ₃
	CDT (a and b)	-2-(3-fluoropyrazinyl)	-CH ₂ CF ₃
	CDU	-2-(3-fluoropyrazinyl)	-OCF ₃

5	CDV (a and b)	-2-(3-fluoropyrazinyl)	-Cl
	CDW (a and b)	-2-(3-fluoropyrazinyl)	-Br
	CDX (a and b)	-2-(3-fluoropyrazinyl)	-I
	CDY (a and b)	-2-(3-fluoropyrazinyl)	-n-butyl
	CDZ (a and b)	-2-(3-fluoropyrazinyl)	-n-propyl
10	CEA (a and b)	-3-(4-chloropyridazinyl)	-t-butyl
	CEB (a and b)	-3-(4-chloropyridazinyl)	-iso-butyl
	CEC (a and b)	-3-(4-chloropyridazinyl)	-sec-butyl
	CED (a and b)	-3-(4-chloropyridazinyl)	-cyclohexyl
	CEE (a and b)	-3-(4-chloropyridazinyl)	-t-butoxy
15	CEF (a and b)	-3-(4-chloropyridazinyl)	-isopropoxy
	CEG (a and b)	-3-(4-chloropyridazinyl)	-CF ₃
	CEH (a and b)	-3-(4-chloropyridazinyl)	-CH ₂ CF ₃
	CEI (a and b)	-3-(4-chloropyridazinyl)	-OCF ₃
	CEJ (a and b)	-3-(4-chloropyridazinyl)	-Cl
20	CEK (a and b)	-3-(4-chloropyridazinyl)	-Br
	CEL (a and b)	-3-(4-chloropyridazinyl)	-I
	CEM (a and b)	-3-(4-chloropyridazinyl)	-n-butyl
	CEN (a and b)	-3-(4-chloropyridazinyl)	-n-propyl
	CEO (a and b)	-3-(4-methylpyridazinyl)	-t-butyl
25	CEP (a and b)	-3-(4-methylpyridazinyl)	-iso-butyl
	CEQ (a and b)	-3-(4-methylpyridazinyl)	-sec-butyl
	CER (a and b)	-3-(4-methylpyridazinyl)	-cyclohexyl
	CES (a and b)	-3-(4-methylpyridazinyl)	-t-butoxy
	CET (a and b)	-3-(4-methylpyridazinyl)	-isopropoxy
	CEU (a and b)	-3-(4-methylpyridazinyl)	-CF ₃
	CEV (a and b)	-3-(4-methylpyridazinyl)	-CH ₂ CF ₃
	CEW (a and b)	-3-(4-methylpyridazinyl)	-OCF ₃
	CEX (a and b)	-3-(4-methylpyridazinyl)	-Cl

5	CEY (a and b)	-3-(4-methylpyridazinyl)	-Br
	CEZ (a and b)	-3-(4-methylpyridazinyl)	-I
	CFA (a and b)	-3-(4-methylpyridazinyl)	-n-butyl
	CFB (a and b)	-3-(4-methylpyridazinyl)	-n-propyl
	CFC (a and b)	-3-(4-fluoropyridazinyl)	-t-butyl
10	CFD (a and b)	-3-(4-fluoropyridazinyl)	-iso-butyl
	CFE (a and b)	-3-(4-fluoropyridazinyl)	-sec-butyl
	CFF (a and b)	-3-(4-fluoropyridazinyl)	-cyclohexyl
	CFG (a and b)	-3-(4-fluoropyridazinyl)	-t-butoxy
	CFH (a and b)	-3-(4-fluoropyridazinyl)	-isopropoxy
15	CFI (a and b)	-3-(4-fluoropyridazinyl)	-CF ₃
	CFJ (a and b)	-3-(4-fluoropyridazinyl)	-CH ₂ CF ₃
	CFK (a and b)	-3-(4-fluoropyridazinyl)	-OCF ₃
	CFL (a and b)	-3-(4-fluoropyridazinyl)	-Cl
	CFM (a and b)	-3-(4-fluoropyridazinyl)	-Br
20	CFN (a and b)	-3-(4-fluoropyridazinyl)	-I
	CFO (a and b)	-3-(4-fluoropyridazinyl)	-n-butyl
	CFP (a and b)	-3-(4-fluoropyridazinyl)	-n-propyl
	CFQ (a and b)	-5-(4-chlorothiadiazolyl)	-t-butyl
	CFR (a and b)	-5-(4-chlorothiadiazolyl)	-iso-butyl
25	CFS (a and b)	-5-(4-chlorothiadiazolyl)	-sec-butyl
	CFT (a and b)	-5-(4-chlorothiadiazolyl)	-cyclohexyl
	CFU (a and b)	-5-(4-chlorothiadiazolyl)	-t-butoxy
	CFV (a and b)	-5-(4-chlorothiadiazolyl)	-isopropoxy
	CFW (a and b)	-5-(4-chlorothiadiazolyl)	-CF ₃
	CFX (a and b)	-5-(4-chlorothiadiazolyl)	-CH ₂ CF ₃
	CFY (a and b)	-5-(4-chlorothiadiazolyl)	-OCF ₃
	CFZ (a and b)	-5-(4-chlorothiadiazolyl)	-Cl
	CGA (a and b)	-5-(4-chlorothiadiazolyl)	-Br

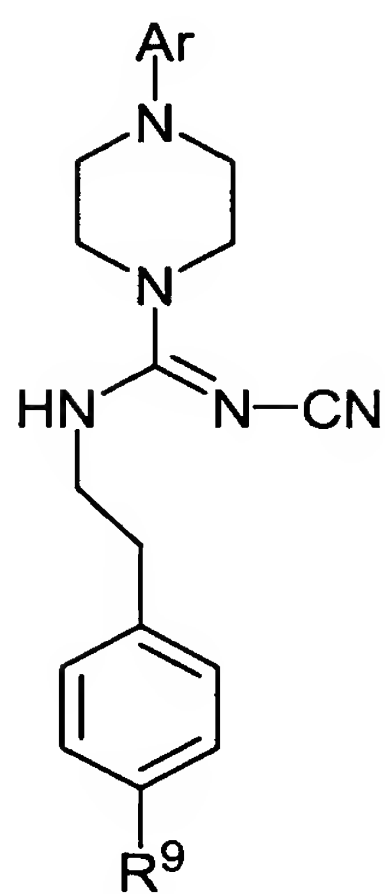
5	CGB (a and b)	-5-(4-chlorothiadiazolyl)	-I
	CGC (a and b)	-5-(4-chlorothiadiazolyl)	-n-butyl
	CGD (a and b)	-5-(4-chlorothiadiazolyl)	-n-propyl
	CGE (a and b)	-5-(4-methylthiadiazolyl)	-t-butyl
	CGF (a and b)	-5-(4-methylthiadiazolyl)	-iso-butyl
10	CGG (a and b)	-5-(4-methylthiadiazolyl)	-sec-butyl
	CGH (a and b)	-5-(4-methylthiadiazolyl)	-cyclohexyl
	CGI (a and b)	-5-(4-methylthiadiazolyl)	-t-butoxy
	CGJ (a and b)	-5-(4-methylthiadiazolyl)	-isopropoxy
	CGK (a and b)	-5-(4-methylthiadiazolyl)	-CF ₃
15	CGL (a and b)	-5-(4-methylthiadiazolyl)	-CH ₂ CF ₃
	CGM (a and b)	-5-(4-methylthiadiazolyl)	-OCF ₃
	CGN (a and b)	-5-(4-methylthiadiazolyl)	-Cl
	CGO (a and b)	-5-(4-methylthiadiazolyl)	-Br
	CGP (a and b)	-5-(4-methylthiadiazolyl)	-I
20	CGQ (a and b)	-5-(4-methylthiadiazolyl)	-n-butyl
	CGR (a and b)	-5-(4-methylthiadiazolyl)	-n-propyl
	CGS (a and b)	-5-(4-fluorothiadiazolyl)	-t-butyl
	CGT (a and b)	-5-(4-fluorothiadiazolyl)	-iso-butyl
	CGU (a and b)	-5-(4-fluorothiadiazolyl)	-sec-butyl
25	CGV (a and b)	-5-(4-fluorothiadiazolyl)	-cyclohexyl
	CGW (a and b)	-5-(4-fluorothiadiazolyl)	-t-butoxy
	CGX (a and b)	-5-(4-fluorothiadiazolyl)	-isopropoxy
	CGY (a and b)	-5-(4-fluorothiadiazolyl)	-CF ₃
	CGZ (a and b)	-5-(4-fluorothiadiazolyl)	-CH ₂ CF ₃
	CHA (a and b)	-5-(4-fluorothiadiazolyl)	-OCF ₃
	CHB (a and b)	-5-(4-fluorothiadiazolyl)	-Cl
	CHC (a and b)	-5-(4-fluorothiadiazolyl)	-Br
	CHD (a and b)	-5-(4-fluorothiadiazolyl)	-I

CHE (a and b)	-5-(4-fluorothiadiazolyl)	-n-butyl
CHF (a and b)	-5-(4-fluorothiadiazolyl)	-n-propyl

wherein “a” means that the carbon atom of the piperazino group to which the methyl group is attached is in the R configuration and “b” means that the carbon of the

5 piperazino group to which the methyl group is attached is in the S configuration

Table 6



XI

and pharmaceutically acceptable salts thereof, wherein:

Compound	Ar	R⁹
CHG	-2-(3-chloropyridyl)	-t-butyl
CHH	-2-(3-chloropyridyl)	-iso-butyl
CHI	-2-(3-chloropyridyl)	-sec-butyl
CHJ	-2-(3-chloropyridyl)	-cyclohexyl
CHK	-2-(3-chloropyridyl)	-t-butoxy
CHL	-2-(3-chloropyridyl)	-isopropoxy
CHM	-2-(3-chloropyridyl)	-CF ₃
CHN	-2-(3-chloropyridyl)	-CH ₂ CF ₃
CHO	-2-(3-chloropyridyl)	-OCF ₃
CHP	-2-(3-chloropyridyl)	-Cl
CHQ	-2-(3-chloropyridyl)	-Br
CHR	-2-(3-chloropyridyl)	-I
CHS	-2-(3-chloropyridyl)	-n-butyl
CHT	-2-(3-chloropyridyl)	-n-propyl
CHU	-2-(3-fluoropyridyl)	-t-butyl

5	CHV	-2-(3-fluoropyridyl)	-iso-butyl
	CHW	-2-(3-fluoropyridyl)	-sec-butyl
	CHX	-2-(3-fluoropyridyl)	-cyclohexyl
	CHY	-2-(3-fluoropyridyl)	-t-butoxy
	CHZ	-2-(3-fluoropyridyl)	-isopropoxy
10	CIA	-2-(3-fluoropyridyl)	-CF ₃
	CIB	-2-(3-fluoropyridyl)	-CH ₂ CF ₃
	CIC	-2-(3-fluoropyridyl)	-OCF ₃
	CID	-2-(3-fluoropyridyl)	-Cl
	CIE	-2-(3-fluoropyridyl)	-Br
15	CIF	-2-(3-fluoropyridyl)	-I
	CIG	-2-(3-fluoropyridyl)	-n-butyl
	CIH	-2-(3-fluoropyridyl)	-n-propyl
	CII	-2-(3-methylpyridyl)	-t-butyl
	CIJ	-2-(3-methylpyridyl)	-iso-butyl
20	CIK	-2-(3-methylpyridyl)	-sec-butyl
	CIL	-2-(3-methylpyridyl)	-cyclohexyl
	CIM	-2-(3-methylpyridyl)	-t-butoxy
	CIN	-2-(3-methylpyridyl)	-isopropoxy
	CIO	-2-(3-methylpyridyl)	-CF ₃
25	CIP	-2-(3-methylpyridyl)	-CH ₂ CF ₃
	CIQ	-2-(3-methylpyridyl)	-OCF ₃
	CIR	-2-(3-methylpyridyl)	-Cl
	CIS	-2-(3-methylpyridyl)	-Br
	CIT	-2-(3-methylpyridyl)	-I
	CIU	-2-(3-methylpyridyl)	-n-butyl
	CIV	-2-(3-methylpyridyl)	-n-propyl
	CIW	-2-(3-CF ₃ -pyridyl)	-t-butyl
	CIX	-2-(3-CF ₃ -pyridyl)	-iso-butyl

5	CIY	-2-(3-CF ₃ -pyridyl)	-sec-butyl
	CIZ	-2-(3-CF ₃ -pyridyl)	-cyclohexyl
	CJA	-2-(3-CF ₃ -pyridyl)	-t-butoxy
	CJB	-2-(3-CF ₃ -pyridyl)	-isopropoxy
	CJC	-2-(3-CF ₃ -pyridyl)	-CF ₃
10	CJD	-2-(3-CF ₃ -pyridyl)	-CH ₂ CF ₃
	CJE	-2-(3-CF ₃ -pyridyl)	-OCF ₃
	CJF	-2-(3-CF ₃ -pyridyl)	-Cl
	CJG	-2-(3-CF ₃ -pyridyl)	-Br
	CJH	-2-(3-CF ₃ -pyridyl)	-I
15	CJI	-2-(3-CF ₃ -pyridyl)	-n-butyl
	CJJ	-2-(3-CF ₃ -pyridyl)	-n-propyl
	CJK	-2-(3-CHF ₂ -pyridyl)	-t-butyl
	CJL	-2-(3-CHF ₂ -pyridyl)	-iso-butyl
	CJM	-2-(3-CHF ₂ -pyridyl)	-sec-butyl
20	CJN	-2-(3-CHF ₂ -pyridyl)	-cyclohexyl
	CJO	-2-(3-CHF ₂ -pyridyl)	-t-butoxy
	CJP	-2-(3-CHF ₂ -pyridyl)	-isopropoxy
	CJQ	-2-(3-CHF ₂ -pyridyl)	-CF ₃
	CJR	-2-(3-CHF ₂ -pyridyl)	-CH ₂ CF ₃
25	CJS	-2-(3-CHF ₂ -pyridyl)	-OCF ₃
	CJT	-2-(3-CHF ₂ -pyridyl)	-Cl
	CJU	-2-(3-CHF ₂ -pyridyl)	-Br
	CJV	-2-(3-CHF ₂ -pyridyl)	-I
	CJW	-2-(3-CHF ₂ -pyridyl)	-n-butyl
	CJX	-2-(3-CHF ₂ -pyridyl)	-n-propyl
	CJY	-2-(3-hydroxypyridyl)	-t-butyl
	CJZ	-2-(3-hydroxypyridyl)	-iso-butyl
	CKA	-2-(3-hydroxypyridyl)	-sec-butyl

5	CKB	-2-(3-hydroxypyridyl)	-cyclohexyl
	CKC	-2-(3-hydroxypyridyl)	-t-butoxy
	CKD	-2-(3-hydroxypyridyl)	-isopropoxy
	CKE	-2-(3-hydroxypyridyl)	-CF ₃
	CKF	-2-(3-hydroxypyridyl)	-CH ₂ CF ₃
10	CKG	-2-(3-hydroxypyridyl)	-OCF ₃
	CKH	-2-(3-hydroxypyridyl)	-Cl
	CKI	-2-(3-hydroxypyridyl)	-Br
	CKJ	-2-(3-hydroxypyridyl)	-I
	CKK	-2-(3-hydroxypyridyl)	-n-butyl
15	CKL	-2-(3-hydroxypyridyl)	-n-propyl
	CKM	-2-(3-nitropyridyl)	-t-butyl
	CKN	-2-(3-nitropyridyl)	-iso-butyl
	CKO	-2-(3-nitropyridyl)	-sec-butyl
	CKP	-2-(3-nitropyridyl)	-cyclohexyl
20	CKQ	-2-(3-nitropyridyl)	-t-butoxy
	CKR	-2-(3-nitropyridyl)	-isopropoxy
	CKS	-2-(3-nitropyridyl)	-CF ₃
	CKT	-2-(3-nitropyridyl)	-CH ₂ CF ₃
	CKU	-2-(3-nitropyridyl)	-OCF ₃
25	CKV	-2-(3-nitropyridyl)	-Cl
	CKW	-2-(3-nitropyridyl)	-Br
	CKX	-2-(3-nitropyridyl)	-I
	CKY	-2-(3-nitropyridyl)	-n-butyl
	CKZ	-2-(3-nitropyridyl)	-n-propyl
	CLA	-2-(3-cyanopyridyl)	-t-butyl
	CLB	-2-(3-cyanopyridyl)	-iso-butyl
	CLC	-2-(3-cyanopyridyl)	-sec-butyl
	CLD	-2-(3-cyanopyridyl)	-cyclohexyl

5	CLE	-2-(3-cyanopyridyl)	-t-butoxy
	CLF	-2-(3-cyanopyridyl)	-isopropoxy
	CLG	-2-(3-cyanopyridyl)	-CF ₃
	CLH	-2-(3-cyanopyridyl)	-CH ₂ CF ₃
	CLI	-2-(3-cyanopyridyl)	-OCF ₃
10	CLJ	-2-(3-cyanopyridyl)	-Cl
	CLK	-2-(3-cyanopyridyl)	-Br
	CLL	-2-(3-cyanopyridyl)	-I
	CLM	-2-(3-cyanopyridyl)	-n-butyl
	CLN	-2-(3-cyanopyridyl)	-n-propyl
15	CLO	-2-(3-bromopyridyl)	-t-butyl
	CLP	-2-(3-bromopyridyl)	-iso-butyl
	CLQ	-2-(3-bromopyridyl)	-sec-butyl
	CLR	-2-(3-bromopyridyl)	-cyclohexyl
	CLS	-2-(3-bromopyridyl)	-t-butoxy
20	CLT	-2-(3-bromopyridyl)	-isopropoxy
	CLU	-2-(3-bromopyridyl)	-CF ₃
	CLV	-2-(3-bromopyridyl)	-CH ₂ CF ₃
	CLW	-2-(3-bromopyridyl)	-OCF ₃
	CLX	-2-(3-bromopyridyl)	-Cl
25	CLY	-2-(3-bromopyridyl)	-Br
	CLZ	-2-(3-bromopyridyl)	-I
	CMA	-2-(3-bromopyridyl)	-n-butyl
	CMB	-2-(3-bromopyridyl)	-n-propyl
	CMC	-2-(3-iodopyridyl)	-t-butyl
	CMD	-2-(3-iodopyridyl)	-iso-butyl
	CME	-2-(3-iodopyridyl)	-sec-butyl
	CMF	-2-(3-iodopyridyl)	-cyclohexyl
	CMG	-2-(3-iodopyridyl)	-t-butoxy

5	CMH	-2-(3-iodopyridyl)	-isopropoxy
	CMI	-2-(3-iodopyridyl)	-CF ₃
	CMJ	-2-(3-iodopyridyl)	-CH ₂ CF ₃
	CMK	-2-(3-iodopyridyl)	-OCF ₃
	CML	-2-(3-iodopyridyl)	-Cl
10	CMM	-2-(3-iodopyridyl)	-Br
	CMN	-2-(3-iodopyridyl)	-I
	CMO	-2-(3-iodopyridyl)	-n-butyl
	CMP	-2-(3-iodopyridyl)	-n-propyl
	CMQ	-4-(5-chloropyrimidinyl)	-t-butyl
15	CMR	-4-(5-chloropyrimidinyl)	-iso-butyl
	CMS	-4-(5-chloropyrimidinyl)	-sec-butyl
	CMT	-4-(5-chloropyrimidinyl)	-cyclohexyl
	CMU	-4-(5-chloropyrimidinyl)	-t-butoxy
	CMV	-4-(5-chloropyrimidinyl)	-isopropoxy
20	CMW	-4-(5-chloropyrimidinyl)	-CF ₃
	CMX	-4-(5-chloropyrimidinyl)	-CH ₂ CF ₃
	CMY	-4-(5-chloropyrimidinyl)	-OCF ₃
	CMZ	-4-(5-chloropyrimidinyl)	-Cl
	CNA	-4-(5-chloropyrimidinyl)	-Br
25	CNB	-4-(5-chloropyrimidinyl)	-I
	CNC	-4-(5-chloropyrimidinyl)	-n-butyl
	CND	-4-(5-chloropyrimidinyl)	-n-propyl
	CNE	-4-(5-methylpyrimidinyl)	-t-butyl
	CNF	-4-(5-methylpyrimidinyl)	-iso-butyl
	CNG	-4-(5-methylpyrimidinyl)	-sec-butyl
	CNH	-4-(5-methylpyrimidinyl)	-cyclohexyl
	CNI	-4-(5-methylpyrimidinyl)	-t-butoxy
	CNJ	-4-(5-methylpyrimidinyl)	-isopropoxy

5	CNK	-4-(5-methylpyrimidinyl)	-CF ₃
	CNL	-4-(5-methylpyrimidinyl)	-CH ₂ CF ₃
	CNM	-4-(5-methylpyrimidinyl)	-OCF ₃
	CNN	-4-(5-methylpyrimidinyl)	-Cl
	CNO	-4-(5-methylpyrimidinyl)	-Br
10	CNP	-4-(5-methylpyrimidinyl)	-I
	CNQ	-4-(5-methylpyrimidinyl)	-n-butyl
	CNR	-4-(5-methylpyrimidinyl)	-n-propyl
	CNS	-4-(5-fluoropyrimidinyl)	-t-butyl
	CNT	-4-(5-fluoropyrimidinyl)	-iso-butyl
15	CNU	-4-(5-fluoropyrimidinyl)	-sec-butyl
	CNV	-4-(5-fluoropyrimidinyl)	-cyclohexyl
	CNW	-4-(5-fluoropyrimidinyl)	-t-butoxy
	CNX	-4-(5-fluoropyrimidinyl)	-isopropoxy
	CNY	-4-(5-fluoropyrimidinyl)	-CF ₃
20	CNZ	-4-(5-fluoropyrimidinyl)	-CH ₂ CF ₃
	COA	-4-(5-fluoropyrimidinyl)	-OCF ₃
	COB	-4-(5-fluoropyrimidinyl)	-Cl
	COC	-4-(5-fluoropyrimidinyl)	-Br
	COD	-4-(5-fluoropyrimidinyl)	-I
25	COE	-4-(5-fluoropyrimidinyl)	-n-butyl
	COF	-4-(5-fluoropyrimidinyl)	-n-propyl
	COG	-2-(3-chloropyrazinyl)	-t-butyl
	COH	-2-(3-chloropyrazinyl)	-iso-butyl
	COI	-2-(3-chloropyrazinyl)	-sec-butyl
	COJ	-2-(3-chloropyrazinyl)	-cyclohexyl
	COK	-2-(3-chloropyrazinyl)	-t-butoxy
	COL	-2-(3-chloropyrazinyl)	-isopropoxy
	COM	-2-(3-chloropyrazinyl)	-CF ₃

5	CON	-2-(3-chloropyrazinyl)	-CH ₂ CF ₃
	COO	-2-(3-chloropyrazinyl)	-OCF ₃
	COP	-2-(3-chloropyrazinyl)	-Cl
	COQ	-2-(3-chloropyrazinyl)	-Br
	COR	-2-(3-chloropyrazinyl)	-I
10	COS	-2-(3-chloropyrazinyl)	-n-butyl
	COT	-2-(3-chloropyrazinyl)	-n-propyl
	COU	-2-(3-methylpyrazinyl)	-t-butyl
	COV	-2-(3-methylpyrazinyl)	-iso-butyl
	COW	-2-(3-methylpyrazinyl)	-sec-butyl
15	COX	-2-(3-methylpyrazinyl)	-cyclohexyl
	COY	-2-(3-methylpyrazinyl)	-t-butoxy
	COZ	-2-(3-methylpyrazinyl)	-isopropoxy
	CPA	-2-(3-methylpyrazinyl)	-CF ₃
	CPB	-2-(3-methylpyrazinyl)	-CH ₂ CF ₃
20	CPC	-2-(3-methylpyrazinyl)	-OCF ₃
	CPD	-2-(3-methylpyrazinyl)	-Cl
	CPE	-2-(3-methylpyrazinyl)	-Br
	CPF	-2-(3-methylpyrazinyl)	-I
	CPG	-2-(3-methylpyrazinyl)	-n-butyl
25	CPH	-2-(3-methylpyrazinyl)	-n-propyl
	CPI	-2-(3-fluoropyrazinyl)	-t-butyl
	CPJ	-2-(3-fluoropyrazinyl)	-iso-butyl
	CPK	-2-(3-fluoropyrazinyl)	-sec-butyl
	CPL	-2-(3-fluoropyrazinyl)	-cyclohexyl
	CPM	-2-(3-fluoropyrazinyl)	-t-butoxy
	CPN	-2-(3-fluoropyrazinyl)	-isopropoxy
	CPO	-2-(3-fluoropyrazinyl)	-CF ₃
	CPP	-2-(3-fluoropyrazinyl)	-CH ₂ CF ₃

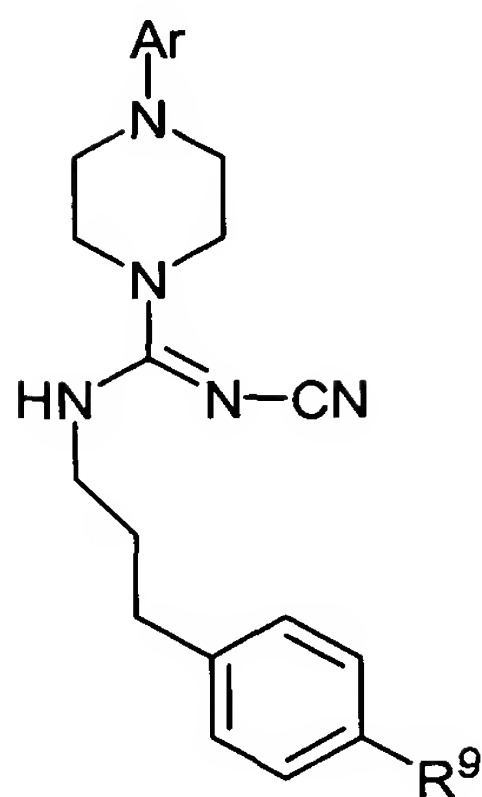
5	CPQ	-2-(3-fluoropyrazinyl)	-OCF ₃
	CPR	-2-(3-fluoropyrazinyl)	-Cl
	CPS	-2-(3-fluoropyrazinyl)	-Br
	CPT	-2-(3-fluoropyrazinyl)	-I
	CPU	-2-(3-fluoropyrazinyl)	-n-butyl
10	CPV	-2-(3-fluoropyrazinyl)	-n-propyl
	CPW	-3-(4-chloropyridazinyl)	-t-butyl
	CPX	-3-(4-chloropyridazinyl)	-iso-butyl
	CPY	-3-(4-chloropyridazinyl)	-sec-butyl
	CPZ	-3-(4-chloropyridazinyl)	-cyclohexyl
15	CQA	-3-(4-chloropyridazinyl)	-t-butoxy
	CQB	-3-(4-chloropyridazinyl)	-isopropoxy
	CQC	-3-(4-chloropyridazinyl)	-CF ₃
	CQD	-3-(4-chloropyridazinyl)	-CH ₂ CF ₃
	CQE	-3-(4-chloropyridazinyl)	-OCF ₃
20	CQF	-3-(4-chloropyridazinyl)	-Cl
	CQG	-3-(4-chloropyridazinyl)	-Br
	CQH	-3-(4-chloropyridazinyl)	-I
	CQI	-3-(4-chloropyridazinyl)	-n-butyl
	CQJ	-3-(4-chloropyridazinyl)	-n-propyl
25	CQK	-3-(4-methylpyridazinyl)	-t-butyl
	CQL	-3-(4-methylpyridazinyl)	-iso-butyl
	CQM	-3-(4-methylpyridazinyl)	-sec-butyl
	CQN	-3-(4-methylpyridazinyl)	-cyclohexyl
	CQO	-3-(4-methylpyridazinyl)	-t-butoxy
	CQP	-3-(4-methylpyridazinyl)	-isopropoxy
	CQQ	-3-(4-methylpyridazinyl)	-CF ₃
	CQR	-3-(4-methylpyridazinyl)	-CH ₂ CF ₃
	CQS	-3-(4-methylpyridazinyl)	-OCF ₃

5	CQT	-3-(4-methylpyridazinyl)	-Cl
	CQU	-3-(4-methylpyridazinyl)	-Br
	CQV	-3-(4-methylpyridazinyl)	-I
	CQW	-3-(4-methylpyridazinyl)	-n-butyl
	CQX	-3-(4-methylpyridazinyl)	-n-propyl
10	CQY	-3-(4-fluoropyridazinyl)	-t-butyl
	CQZ	-3-(4-fluoropyridazinyl)	-iso-butyl
	CRA	-3-(4-fluoropyridazinyl)	-sec-butyl
	CRB	-3-(4-fluoropyridazinyl)	-cyclohexyl
	CRC	-3-(4-fluoropyridazinyl)	-t-butoxy
15	CRD	-3-(4-fluoropyridazinyl)	-isopropoxy
	CRE	-3-(4-fluoropyridazinyl)	-CF ₃
	CRF	-3-(4-fluoropyridazinyl)	-CH ₂ CF ₃
	CRG	-3-(4-fluoropyridazinyl)	-OCF ₃
	CRH	-3-(4-fluoropyridazinyl)	-Cl
20	CRI	-3-(4-fluoropyridazinyl)	-Br
	CRJ	-3-(4-fluoropyridazinyl)	-I
	CRK	-3-(4-fluoropyridazinyl)	-n-butyl
	CRL	-3-(4-fluoropyridazinyl)	-n-propyl
	CRM	-5-(4-chlorothiadiazo- lyl)	-t-butyl
25	CRN	-5-(4-chlorothiadiazo- lyl)	-iso-butyl
	CRO	-5-(4-chlorothiadiazo- lyl)	-sec-butyl
	CRP	-5-(4-chlorothiadiazo- lyl)	-cyclohexyl
	CRQ	-5-(4-chlorothiadiazo- lyl)	-t-butoxy
	CRR	-5-(4-chlorothiadiazo- lyl)	-isopropoxy
	CRS	-5-(4-chlorothiadiazo- lyl)	-CF ₃
	CRT	-5-(4-chlorothiadiazo- lyl)	-CH ₂ CF ₃
	CRU	-5-(4-chlorothiadiazo- lyl)	-OCF ₃
	CRV	-5-(4-chlorothiadiazo- lyl)	-Cl

5	CRW	-5-(4-chlorothiadiazolyl)	-Br
	CRX	-5-(4-chlorothiadiazolyl)	-I
	CRY	-5-(4-chlorothiadiazolyl)	-n-butyl
	CRZ	-5-(4-chlorothiadiazolyl)	-n-propyl
	CSA	-5-(4-methylthiadiazolyl)	-t-butyl
10	CSB	-5-(4-methylthiadiazolyl)	-iso-butyl
	CSC	-5-(4-methylthiadiazolyl)	-sec-butyl
	CSD	-5-(4-methylthiadiazolyl)	-cyclohexyl
	CSE	-5-(4-methylthiadiazolyl)	-t-butoxy
	CSF	-5-(4-methylthiadiazolyl)	-isopropoxy
15	CSG	-5-(4-methylthiadiazolyl)	-CF ₃
	CSH	-5-(4-methylthiadiazolyl)	-CH ₂ CF ₃
	CSI	-5-(4-methylthiadiazolyl)	-OCF ₃
	CSJ	-5-(4-methylthiadiazolyl)	-Cl
	CSK	-5-(4-methylthiadiazolyl)	-Br
20	CSL	-5-(4-methylthiadiazolyl)	-I
	CSM	-5-(4-methylthiadiazolyl)	-n-butyl
	CSN	-5-(4-methylthiadiazolyl)	-n-propyl
	CSO	-5-(4-fluorothiadiazolyl)	-t-butyl
	CSP	-5-(4-fluorothiadiazolyl)	-iso-butyl
25	CSQ	-5-(4-fluorothiadiazolyl)	-sec-butyl
	CSR	-5-(4-fluorothiadiazolyl)	-cyclohexyl
	CSS	-5-(4-fluorothiadiazolyl)	-t-butoxy
	CST	-5-(4-fluorothiadiazolyl)	-isopropoxy
	CSU	-5-(4-fluorothiadiazolyl)	-CF ₃
	CSV	-5-(4-fluorothiadiazolyl)	-CH ₂ CF ₃
	CSW	-5-(4-fluorothiadiazolyl)	-OCF ₃
	CSX	-5-(4-fluorothiadiazolyl)	-Cl
	CSY	-5-(4-fluorothiadiazolyl)	-Br

CSZ	-5-(4-fluorothiadiazolyl)	-I
CTA	-5-(4-fluorothiadiazolyl)	-n-butyl
CTB	-5-(4-fluorothiadiazolyl)	-n-propyl

Table 7



and pharmaceutically acceptable salts thereof, wherein:

Compound	Ar	R ⁹
CTC	-2-(3-chloropyridyl)	-t-butyl
CTD	-2-(3-chloropyridyl)	-iso-butyl
CTE	-2-(3-chloropyridyl)	-sec-butyl
CTF	-2-(3-chloropyridyl)	-cyclohexyl
CTG	-2-(3-chloropyridyl)	-t-butoxy
CTH	-2-(3-chloropyridyl)	-isopropoxy
CTI	-2-(3-chloropyridyl)	-CF ₃
CTJ	-2-(3-chloropyridyl)	-CH ₂ CF ₃
CTK	-2-(3-chloropyridyl)	-OCF ₃
CTL	-2-(3-chloropyridyl)	-Cl
CTM	-2-(3-chloropyridyl)	-Br
CTN	-2-(3-chloropyridyl)	-I
CTO	-2-(3-chloropyridyl)	-n-butyl
CTP	-2-(3-chloropyridyl)	-n-propyl
CTQ	-2-(3-fluoropyridyl)	-t-butyl
CTR	-2-(3-fluoropyridyl)	-iso-butyl
CTS	-2-(3-fluoropyridyl)	-sec-butyl
CTT	-2-(3-fluoropyridyl)	-cyclohexyl

5	CTU	-2-(3-fluoropyridyl)	-t-butoxy
	CTV	-2-(3-fluoropyridyl)	-isopropoxy
	CTW	-2-(3-fluoropyridyl)	-CF ₃
	CTX	-2-(3-fluoropyridyl)	-CH ₂ CF ₃
	CTY	-2-(3-fluoropyridyl)	-OCF ₃
10	CTZ	-2-(3-fluoropyridyl)	-Cl
	CUA	-2-(3-fluoropyridyl)	-Br
	CUB	-2-(3-fluoropyridyl)	-I
	CUC	-2-(3-fluoropyridyl)	-n-butyl
	CUD	-2-(3-fluoropyridyl)	-n-propyl
15	CUE	-2-(3-methylpyridyl)	-t-butyl
	CUF	-2-(3-methylpyridyl)	-iso-butyl
	CUG	-2-(3-methylpyridyl)	-sec-butyl
	CUH	-2-(3-methylpyridyl)	-cyclohexyl
	CUI	-2-(3-methylpyridyl)	-t-butoxy
20	CUJ	-2-(3-methylpyridyl)	-isopropoxy
	CUK	-2-(3-methylpyridyl)	-CF ₃
	CUL	-2-(3-methylpyridyl)	-CH ₂ CF ₃
	CUM	-2-(3-methylpyridyl)	-OCF ₃
	CUN	-2-(3-methylpyridyl)	-Cl
25	CUO	-2-(3-methylpyridyl)	-Br
	CUP	-2-(3-methylpyridyl)	-I
	CUQ	-2-(3-methylpyridyl)	-n-butyl
	CUR	-2-(3-methylpyridyl)	-n-propyl
	CUS	-2-(3-CF ₃ -pyridyl)	-t-butyl
	CUT	-2-(3-CF ₃ -pyridyl)	-iso-butyl
	CUU	-2-(3-CF ₃ -pyridyl)	-sec-butyl
	CUV	-2-(3-CF ₃ -pyridyl)	-cyclohexyl
	CUW	-2-(3-CF ₃ -pyridyl)	-t-butoxy

5	CUX	-2-(3-CF ₃ -pyridyl)	-isopropoxy
	CUY	-2-(3-CF ₃ -pyridyl)	-CF ₃
	CUZ	-2-(3-CF ₃ -pyridyl)	-CH ₂ CF ₃
	CVA	-2-(3-CF ₃ -pyridyl)	-OCF ₃
	CVB	-2-(3-CF ₃ -pyridyl)	-Cl
10	CVC	-2-(3-CF ₃ -pyridyl)	-Br
	CVD	-2-(3-CF ₃ -pyridyl)	-I
	CVE	-2-(3-CF ₃ -pyridyl)	-n-butyl
	CVF	-2-(3-CF ₃ -pyridyl)	-n-propyl
	CVG	-2-(3-CHF ₂ -pyridyl)	-t-butyl
15	CVH	-2-(3-CHF ₂ -pyridyl)	-iso-butyl
	CVI	-2-(3-CHF ₂ -pyridyl)	-sec-butyl
	CVJ	-2-(3-CHF ₂ -pyridyl)	-cyclohexyl
	CVK	-2-(3-CHF ₂ -pyridyl)	-t-butoxy
	CVL	-2-(3-CHF ₂ -pyridyl)	-isopropoxy
20	CVM	-2-(3-CHF ₂ -pyridyl)	-CF ₃
	CVN	-2-(3-CHF ₂ -pyridyl)	-CH ₂ CF ₃
	CVO	-2-(3-CHF ₂ -pyridyl)	-OCF ₃
	CVP	-2-(3-CHF ₂ -pyridyl)	-Cl
	CVQ	-2-(3-CHF ₂ -pyridyl)	-Br
25	CVR	-2-(3-CHF ₂ -pyridyl)	-I
	CVS	-2-(3-CHF ₂ -pyridyl)	-n-butyl
	CVT	-2-(3-CHF ₂ -pyridyl)	-n-propyl
	CVU	-2-(3-hydroxypyridyl)	-t-butyl
	CVV	-2-(3-hydroxypyridyl)	-iso-butyl
	CVW	-2-(3-hydroxypyridyl)	-sec-butyl
	CVX	-2-(3-hydroxypyridyl)	-cyclohexyl
	CVY	-2-(3-hydroxypyridyl)	-t-butoxy
	CVZ	-2-(3-hydroxypyridyl)	-isopropoxy

5	CWA	-2-(3-hydroxypyridyl)	-CF ₃
	CWB	-2-(3-hydroxypyridyl)	-CH ₂ CF ₃
	CWC	-2-(3-hydroxypyridyl)	-OCF ₃
	CWD	-2-(3-hydroxypyridyl)	-Cl
	CWE	-2-(3-hydroxypyridyl)	-Br
10	CWF	-2-(3-hydroxypyridyl)	-I
	CWG	-2-(3-hydroxypyridyl)	-n-butyl
	CWH	-2-(3-hydroxypyridyl)	-n-propyl
	CWI	-2-(3-nitropyridyl)	-t-butyl
	CWJ	-2-(3-nitropyridyl)	-iso-butyl
15	CWK	-2-(3-nitropyridyl)	-sec-butyl
	CWL	-2-(3-nitropyridyl)	-cyclohexyl
	CWM	-2-(3-nitropyridyl)	-t-butoxy
	CWN	-2-(3-nitropyridyl)	-isopropoxy
	CWO	-2-(3-nitropyridyl)	-CF ₃
20	CWP	-2-(3-nitropyridyl)	-CH ₂ CF ₃
	CWQ	-2-(3-nitropyridyl)	-OCF ₃
	CWR	-2-(3-nitropyridyl)	-Cl
	CWS	-2-(3-nitropyridyl)	-Br
	CWT	-2-(3-nitropyridyl)	-I
25	CWU	-2-(3-nitropyridyl)	-n-butyl
	CWV	-2-(3-nitropyridyl)	-n-propyl
	CWW	-2-(3-cyanopyridyl)	-t-butyl
	CWX	-2-(3-cyanopyridyl)	-iso-butyl
	CWY	-2-(3-cyanopyridyl)	-sec-butyl
	CWZ	-2-(3-cyanopyridyl)	-cyclohexyl
	CXA	-2-(3-cyanopyridyl)	-t-butoxy
	CXB	-2-(3-cyanopyridyl)	-isopropoxy
	CXC	-2-(3-cyanopyridyl)	-CF ₃

5	CXD	-2-(3-cyanopyridyl)	-CH ₂ CF ₃
	CXE	-2-(3-cyanopyridyl)	-OCF ₃
	CXF	-2-(3-cyanopyridyl)	-Cl
	CXG	-2-(3-cyanopyridyl)	-Br
	CXH	-2-(3-cyanopyridyl)	-I
	CXI	-2-(3-cyanopyridyl)	-n-butyl
	CXJ	-2-(3-cyanopyridyl)	-n-propyl
	CXK	-2-(3-bromopyridyl)	-t-butyl
	CXL	-2-(3-bromopyridyl)	-iso-butyl
	CXM	-2-(3-bromopyridyl)	-sec-butyl
10	CXN	-2-(3-bromopyridyl)	-cyclohexyl
	CXO	-2-(3-bromopyridyl)	-t-butoxy
	CXP	-2-(3-bromopyridyl)	-isopropoxy
	CXQ	-2-(3-bromopyridyl)	-CF ₃
	CXR	-2-(3-bromopyridyl)	-CH ₂ CF ₃
15	CXS	-2-(3-bromopyridyl)	-OCF ₃
	CXT	-2-(3-bromopyridyl)	-Cl
	CXU	-2-(3-bromopyridyl)	-Br
	CXV	-2-(3-bromopyridyl)	-I
	CXW	-2-(3-bromopyridyl)	-n-butyl
20	CXX	-2-(3-bromopyridyl)	-n-propyl
	CXY	-2-(3-iodopyridyl)	-t-butyl
	CXZ	-2-(3-iodopyridyl)	-iso-butyl
	CYA	-2-(3-iodopyridyl)	-sec-butyl
	CYB	-2-(3-iodopyridyl)	-cyclohexyl
25	CYC	-2-(3-iodopyridyl)	-t-butoxy
	CYD	-2-(3-iodopyridyl)	-isopropoxy
	CYE	-2-(3-iodopyridyl)	-CF ₃
	CYF	-2-(3-iodopyridyl)	-CH ₂ CF ₃

5	CYG	-2-(3-iodopyridyl)	-OCF ₃
	CYH	-2-(3-iodopyridyl)	-Cl
	CYI	-2-(3-iodopyridyl)	-Br
	CYJ	-2-(3-iodopyridyl)	-I
	CYK	-2-(3-iodopyridyl)	-n-butyl
10	CYL	-2-(3-iodopyridyl)	-n-propyl
	CYM	-4-(5-chloropyrimidinyl)	-t-butyl
	CYN	-4-(5-chloropyrimidinyl)	-iso-butyl
	CYO	-4-(5-chloropyrimidinyl)	-sec-butyl
	CYP	-4-(5-chloropyrimidinyl)	-cyclohexyl
15	CYQ	-4-(5-chloropyrimidinyl)	-t-butoxy
	CYR	-4-(5-chloropyrimidinyl)	-isopropoxy
	CYS	-4-(5-chloropyrimidinyl)	-CF ₃
	CYT	-4-(5-chloropyrimidinyl)	-CH ₂ CF ₃
	CYU	-4-(5-chloropyrimidinyl)	-OCF ₃
20	CYV	-4-(5-chloropyrimidinyl)	-Cl
	CYW	-4-(5-chloropyrimidinyl)	-Br
	CYX	-4-(5-chloropyrimidinyl)	-I
	CYY	-4-(5-chloropyrimidinyl)	-n-butyl
	CYZ	-4-(5-chloropyrimidinyl)	-n-propyl
25	CZA	-4-(5-methylpyrimidinyl)	-t-butyl
	CZB	-4-(5-methylpyrimidinyl)	-iso-butyl
	CZC	-4-(5-methylpyrimidinyl)	-sec-butyl
	CZD	-4-(5-methylpyrimidinyl)	-cyclohexyl
	CZE	-4-(5-methylpyrimidinyl)	-t-butoxy
	CZF	-4-(5-methylpyrimidinyl)	-isopropoxy
	CZG	-4-(5-methylpyrimidinyl)	-CF ₃
	CZH	-4-(5-methylpyrimidinyl)	-CH ₂ CF ₃
	CZI	-4-(5-methylpyrimidinyl)	-OCF ₃

5	CZJ	-4-(5-methylpyrimidinyl)	-Cl
	CZK	-4-(5-methylpyrimidinyl)	-Br
	CZL	-4-(5-methylpyrimidinyl)	-I
	CZM	-4-(5-methylpyrimidinyl)	-n-butyl
	CZN	-4-(5-methylpyrimidinyl)	-n-propyl
10	CZO	-4-(5-fluoropyrimidinyl)	-t-butyl
	CZP	-4-(5-fluoropyrimidinyl)	-iso-butyl
	CZQ	-4-(5-fluoropyrimidinyl)	-sec-butyl
	CZR	-4-(5-fluoropyrimidinyl)	-cyclohexyl
	CZS	-4-(5-fluoropyrimidinyl)	-t-butoxy
15	CZT	-4-(5-fluoropyrimidinyl)	-isopropoxy
	CZU	-4-(5-fluoropyrimidinyl)	-CF ₃
	CZV	-4-(5-fluoropyrimidinyl)	-CH ₂ CF ₃
	CZW	-4-(5-fluoropyrimidinyl)	-OCF ₃
	CZX	-4-(5-fluoropyrimidinyl)	-Cl
20	CZY	-4-(5-fluoropyrimidinyl)	-Br
	CZZ	-4-(5-fluoropyrimidinyl)	-I
	DAA	-4-(5-fluoropyrimidinyl)	-n-butyl
	DAB	-4-(5-fluoropyrimidinyl)	-n-propyl
	DAC	-2-(3-chloropyrazinyl)	-t-butyl
25	DAD	-2-(3-chloropyrazinyl)	-iso-butyl
	DAE	-2-(3-chloropyrazinyl)	-sec-butyl
	DAF	-2-(3-chloropyrazinyl)	-cyclohexyl
	DAG	-2-(3-chloropyrazinyl)	-t-butoxy
	DAH	-2-(3-chloropyrazinyl)	-isopropoxy
	DAI	-2-(3-chloropyrazinyl)	-CF ₃
	DAJ	-2-(3-chloropyrazinyl)	-CH ₂ CF ₃
	DAK	-2-(3-chloropyrazinyl)	-OCF ₃
	DAL	-2-(3-chloropyrazinyl)	-Cl

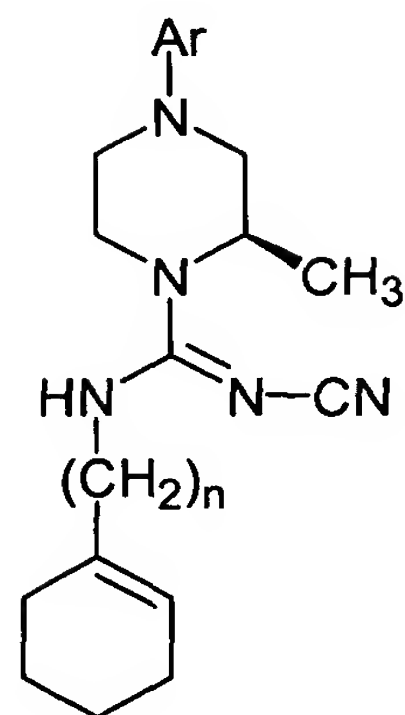
5	DAM	-2-(3-chloropyrazinyl)	-Br
	DAN	-2-(3-chloropyrazinyl)	-I
	DAO	-2-(3-chloropyrazinyl)	-n-butyl
	DAP	-2-(3-chloropyrazinyl)	-n-propyl
	DAQ	-2-(3-methylpyrazinyl)	-t-butyl
10	DAR	-2-(3-methylpyrazinyl)	-iso-butyl
	DAS	-2-(3-methylpyrazinyl)	-sec-butyl
	DAT	-2-(3-methylpyrazinyl)	-cyclohexyl
	DAU	-2-(3-methylpyrazinyl)	-t-butoxy
	DAV	-2-(3-methylpyrazinyl)	-isopropoxy
15	DAW	-2-(3-methylpyrazinyl)	-CF ₃
	DAX	-2-(3-methylpyrazinyl)	-CH ₂ CF ₃
	DAY	-2-(3-methylpyrazinyl)	-OCF ₃
	DAZ	-2-(3-methylpyrazinyl)	-Cl
	DBA	-2-(3-methylpyrazinyl)	-Br
20	DBB	-2-(3-methylpyrazinyl)	-I
	DBC	-2-(3-methylpyrazinyl)	-n-butyl
	DBD	-2-(3-methylpyrazinyl)	-n-propyl
	DBE	-2-(3-fluoropyrazinyl)	-t-butyl
	DBF	-2-(3-fluoropyrazinyl)	-iso-butyl
25	DBG	-2-(3-fluoropyrazinyl)	-sec-butyl
	DBH	-2-(3-fluoropyrazinyl)	-cyclohexyl
	DBI	-2-(3-fluoropyrazinyl)	-t-butoxy
	DBJ	-2-(3-fluoropyrazinyl)	-isopropoxy
	DBK	-2-(3-fluoropyrazinyl)	-CF ₃
	DBL	-2-(3-fluoropyrazinyl)	-CH ₂ CF ₃
	DBM	-2-(3-fluoropyrazinyl)	-OCF ₃
	DBN	-2-(3-fluoropyrazinyl)	-Cl
	DBO	-2-(3-fluoropyrazinyl)	-Br

5	DBP	-2-(3-fluoropyrazinyl)	-I
	DBQ	-2-(3-fluoropyrazinyl)	-n-butyl
	DBR	-2-(3-fluoropyrazinyl)	-n-propyl
	DBS	-3-(4-chloropyridazinyl)	-t-butyl
	DBT	-3-(4-chloropyridazinyl)	-iso-butyl
10	DBU	-3-(4-chloropyridazinyl)	-sec-butyl
	DBV	-3-(4-chloropyridazinyl)	-cyclohexyl
	DBW	-3-(4-chloropyridazinyl)	-t-butoxy
	DBX	-3-(4-chloropyridazinyl)	-isopropoxy
	DBY	-3-(4-chloropyridazinyl)	-CF ₃
15	DBZ	-3-(4-chloropyridazinyl)	-CH ₂ CF ₃
	DCA	-3-(4-chloropyridazinyl)	-OCF ₃
	DCB	-3-(4-chloropyridazinyl)	-Cl
	DCC	-3-(4-chloropyridazinyl)	-Br
	DCD	-3-(4-chloropyridazinyl)	-I
20	DCE	-3-(4-chloropyridazinyl)	-n-butyl
	DCF	-3-(4-chloropyridazinyl)	-n-propyl
	DCG	-3-(4-methylpyridazinyl)	-t-butyl
	DCH	-3-(4-methylpyridazinyl)	-iso-butyl
	DCI	-3-(4-methylpyridazinyl)	-sec-butyl
25	DCJ	-3-(4-methylpyridazinyl)	-cyclohexyl
	DCK	-3-(4-methylpyridazinyl)	-t-butoxy
	DCL	-3-(4-methylpyridazinyl)	-isopropoxy
	DCM	-3-(4-methylpyridazinyl)	-CF ₃
	DCN	-3-(4-methylpyridazinyl)	-CH ₂ CF ₃
	DCO	-3-(4-methylpyridazinyl)	-OCF ₃
	DCP	-3-(4-methylpyridazinyl)	-Cl
	DCQ	-3-(4-methylpyridazinyl)	-Br
	DCR	-3-(4-methylpyridazinyl)	-I

5	DCS	-3-(4-methylpyridazinyl)	-n-butyl
	DCT	-3-(4-methylpyridazinyl)	-n-propyl
	DCU	-3-(4-fluoropyridazinyl)	-t-butyl
	DCV	-3-(4-fluoropyridazinyl)	-iso-butyl
	DCW	-3-(4-fluoropyridazinyl)	-sec-butyl
10	DCX	-3-(4-fluoropyridazinyl)	-cyclohexyl
	DCY	-3-(4-fluoropyridazinyl)	-t-butoxy
	DCZ	-3-(4-fluoropyridazinyl)	-isopropoxy
	DDA	-3-(4-fluoropyridazinyl)	-CF ₃
	DDB	-3-(4-fluoropyridazinyl)	-CH ₂ CF ₃
15	DDC	-3-(4-fluoropyridazinyl)	-OCF ₃
	DDD	-3-(4-fluoropyridazinyl)	-Cl
	DDE	-3-(4-fluoropyridazinyl)	-Br
	DDF	-3-(4-fluoropyridazinyl)	-I
	DDG	-3-(4-fluoropyridazinyl)	-n-butyl
20	DDH	-3-(4-fluoropyridazinyl)	-n-propyl
	DDI	-5-(4-chlorothiadiazo- lyl)	-t-butyl
	DDJ	-5-(4-chlorothiadiazo- lyl)	-iso-butyl
	DDK	-5-(4-chlorothiadiazo- lyl)	-sec-butyl
	DDL	-5-(4-chlorothiadiazo- lyl)	-cyclohexyl
25	DDM	-5-(4-chlorothiadiazo- lyl)	-t-butoxy
	DDN	-5-(4-chlorothiadiazo- lyl)	-isopropoxy
	DDO	-5-(4-chlorothiadiazo- lyl)	-CF ₃
	DDP	-5-(4-chlorothiadiazo- lyl)	-CH ₂ CF ₃
	DDQ	-5-(4-chlorothiadiazo- lyl)	-OCF ₃
	DDR	-5-(4-chlorothiadiazo- lyl)	-Cl
	DDS	-5-(4-chlorothiadiazo- lyl)	-Br
	DDT	-5-(4-chlorothiadiazo- lyl)	-I
	DDU	-5-(4-chlorothiadiazo- lyl)	-n-butyl

5	DDV	-5-(4-chlorothiadiazolyl)	-n-propyl
	DDW	-5-(4-methylthiadiazolyl)	-t-butyl
	DDX	-5-(4-methylthiadiazolyl)	-iso-butyl
	DDY	-5-(4-methylthiadiazolyl)	-sec-butyl
	DDZ	-5-(4-methylthiadiazolyl)	-cyclohexyl
10	DEA	-5-(4-methylthiadiazolyl)	-t-butoxy
	DEB	-5-(4-methylthiadiazolyl)	-isopropoxy
	DEC	-5-(4-methylthiadiazolyl)	-CF ₃
	DED	-5-(4-methylthiadiazolyl)	-CH ₂ CF ₃
	DEE	-5-(4-methylthiadiazolyl)	-OCF ₃
15	DEF	-5-(4-methylthiadiazolyl)	-Cl
	DEG	-5-(4-methylthiadiazolyl)	-Br
	DEH	-5-(4-methylthiadiazolyl)	-I
	DEI	-5-(4-methylthiadiazolyl)	-n-butyl
	DEJ	-5-(4-methylthiadiazolyl)	-n-propyl
20	DEK	-5-(4-fluorothiadiazolyl)	-t-butyl
	DEL	-5-(4-fluorothiadiazolyl)	-iso-butyl
	DEM	-5-(4-fluorothiadiazolyl)	-sec-butyl
	DEN	-5-(4-fluorothiadiazolyl)	-cyclohexyl
	DEO	-5-(4-fluorothiadiazolyl)	-t-butoxy
25	DEP	-5-(4-fluorothiadiazolyl)	-isopropoxy
	DEQ	-5-(4-fluorothiadiazolyl)	-CF ₃
	DER	-5-(4-fluorothiadiazolyl)	-CH ₂ CF ₃
	DES	-5-(4-fluorothiadiazolyl)	-OCF ₃
	DET	-5-(4-fluorothiadiazolyl)	-Cl
	DEU	-5-(4-fluorothiadiazolyl)	-Br
	DEV	-5-(4-fluorothiadiazolyl)	-I
	DEW	-5-(4-fluorothiadiazolyl)	-n-butyl
	DEX	-5-(4-fluorothiadiazolyl)	-n-propyl

Table 8



and pharmaceutically acceptable salts thereof, wherein:

<u>Compound</u>	<u>Ar</u>	<u>n</u>
DEY	-2-(3-chloropyridyl)	2
DEZ	-2-(3-fluoropyridyl)	2
DFA	-2-(3-methylpyridyl)	2
DFB	-2-(3-CF ₃ -pyridyl)	2
DFC	-2-(3-CHF ₂ -pyridyl)	2
DFD	-2-(3-hydroxypyridyl)	2
DFE	-2-(3-nitropyridyl)	2
DFF	-2-(3-cyanopyridyl)	2
DFG	-2-(3-bromopyridyl)	2
DFH	-2-(3-iodopyridyl)	2
DFI	-4-(5-chloropyrimidinyl)	2
DFJ	-4-(5-methylpyrimidinyl)	2
DFK	-4-(5-fluoropyrimidinyl)	2
DFL	-2-(3-chloropyrazinyl)	2
DFM	-2-(3-methylpyrazinyl)	2
DFN	-2-(3-fluoropyrazinyl)	2
DFO	-3-(4-chloropyridazinyl)	2
DFP	-3-(4-methylpyridazinyl)	2

DFQ	-3-(4-fluoropyridazinyl)	2
DFR	-5-(4-chlorothiadiazo-lyl)	2
DFS	-5-(4-methylthiadiazo-lyl)	2
DFT	-5-(4-fluorothiadiazo-lyl)	2

5	DFU	-2-(3-chloropyridyl)	3
	DFV	-2-(3-fluoropyridyl)	3
	DFW	-2-(3-methylpyridyl)	3
	DFX	-2-(3-CF ₃ -pyridyl)	3
	DFY	-2-(3-CHF ₂ -pyridyl)	3
10	DFZ	-2-(3-hydroxypyridyl)	3
	DGA	-2-(3-nitropyridyl)	3
	DGB	-2-(3-cyanopyridyl)	3
	DGC	-2-(3-bromopyridyl)	3
	DGD	-2-(3-iodopyridyl)	3
15	DGE	-4-(5-chloropyrimidinyl)	3
	DGF	-4-(5-methylpyrimidinyl)	3
	DGG	-4-(5-fluoropyrimidinyl)	3
	DGH	-2-(3-chloropyrazinyl)	3
	DGI	-2-(3-methylpyrazinyl)	3
20	DGJ	-2-(3-fluoropyrazinyl)	3
	DGK	-3-(4-chloropyridazinyl)	3
	DGL	-3-(4-methylpyridazinyl)	3
	DGM	-3-(4-fluoropyridazinyl)	3
	DGN	-5-(4-chlorothiadiazo-lyl)	3
25	DGO	-5-(4-methylthiadiazo-lyl)	3
	DGP	-5-(4-fluorothiadiazo-lyl)	3

4.17 DEFINITIONS

As used herein, the terms used above having following meaning:

“(C₁-C₁₀)alkyl” means a straight chain or branched non-cyclic hydrocarbon having from 1 to 10 carbon atoms. Representative straight chain -(C₁-C₁₀)alkyls include
5 -methyl, -ethyl, -n-propyl, -n-butyl, -n-pentyl, -n-hexyl, -n-heptyl, -n-octyl, -n-nonyl and -n-decyl. Representative branched -(C₁-C₁₀)alkyls include -isopropyl, -sec-butyl, -isobutyl, -tert-butyl, -isopentyl, -neopentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1-ethylbutyl, 2-ethylbutyl, 3-ethylbutyl, 1,1-dimethylbutyl,
10 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl and 3,3-dimethylbutyl. -isopropyl, -sec-butyl, -isobutyl, 1-methylhexyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 1,2-dimethylpentyl, 1,3-dimethylpentyl, 1,2-dimethylhexyl, 1,3-dimethylhexyl, 3,3-dimethylhexyl, 1,2-dimethylheptyl, 1,3-dimethylheptyl, and 3,3-dimethylheptyl.

15 “(C₁-C₆)alkyl” means a straight chain or branched non-cyclic hydrocarbon having from 1 to 6 carbon atoms. Representative straight chain -(C₁-C₆)alkyls include -methyl, -ethyl, -n-propyl, -n-butyl, -n-pentyl and -n-hexyl. Representative branched -(C₁-C₆)alkyls include -isopropyl, -sec-butyl, -isobutyl, -tert-butyl, -isopentyl, -neopentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl,
20 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1-ethylbutyl, 2-ethylbutyl, 3-ethylbutyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl and 3,3-dimethylbutyl.

“(C₂-C₁₀)alkenyl” means a straight chain or branched non-cyclic hydrocarbon having from 2 to 10 carbon atoms and including at least one carbon-carbon double bond.
25 Representative straight chain and branched (C₂-C₁₀)alkenyls include -vinyl, -allyl, -1-butenyl, -2-butenyl, -isobutylenyl, -1-pentenyl, -2-pentenyl, -3-methyl-1-butenyl, -2-methyl-2-butenyl, -2,3-dimethyl-2-butenyl, -1-hexenyl, -2-hexenyl, -3-hexenyl, -1-heptenyl, -2-heptenyl, -3-heptenyl, -1-octenyl, -2-octenyl, -3-octenyl, -1-nonenyl, -2-nonenyl, -3-nonenyl, -1-decenyl, -2-decenyl, -3-decenyl and the like.

“(C₂-C₆)alkenyl” means a straight chain or branched non-cyclic hydrocarbon having from 2 to 6 carbon atoms and including at least one carbon-carbon double bond. Representative straight chain and branched (C₂-C₆)alkenyls include -vinyl, -allyl, -1-butenyl, -2-butenyl, -isobutylenyl, -1-pentenyl, -2-pentenyl, -3-methyl-1-butenyl, -2-methyl-2-butenyl, 5 -2,3-dimethyl-2-butenyl, -1-hexenyl, 2-hexenyl, 3-hexenyl and the like.

“(C₂-C₁₀)alkynyl” means a straight chain or branched non-cyclic hydrocarbon having from 2 to 10 carbon atoms and including at least one carbon-carbon triple bond. Representative straight chain and branched (C₂-C₁₀)alkynyls include -acetylenyl, -propynyl, -1-butynyl, -2-butynyl, -1-pentynyl, -2-pentynyl, -3-methyl-1-butynyl, -4-pentynyl, -1- 10 hexynyl, -2-hexynyl, -5-hexynyl, -1-heptynyl, -2-heptynyl, -6-heptynyl, -1-octynyl, -2-octynyl, -7-octynyl, -1-nonyl, -2-nonyl, -8-nonyl, -1-decynyl, -2-decynyl, -9-decynyl and the like.

“(C₂-C₆)alkynyl” means a straight chain or branched non-cyclic hydrocarbon having from 2 to 6 carbon atoms and including at least one carbon-carbon triple bond. 15 Representative straight chain and branched (C₂-C₆)alkynyls include -acetylenyl, -propynyl, -1-butynyl, -2-butynyl, -1-pentynyl, -2-pentynyl, -3-methyl-1-butynyl, -4-pentynyl, -1-hexynyl, -2-hexynyl, -5-hexynyl and the like.

“(C₃-C₁₀)cycloalkyl” means a saturated cyclic hydrocarbon having from 3 to 10 carbon atoms. Representative (C₃-C₁₀)cycloalkyls are -cyclopropyl, -cyclobutyl, 20 -cyclopentyl, -cyclohexyl, -cycloheptyl, -cyclooctyl, -cyclononyl and -cyclodecyl.

“(C₃-C₈)cycloalkyl” means a saturated cyclic hydrocarbon having from 3 to 8 carbon atoms. Representative (C₃-C₈)cycloalkyls include -cyclopropyl, -cyclobutyl, -cyclopentyl, -cyclohexyl, -cycloheptyl and -cyclooctyl.

“(C₈-C₁₄)bicycloalkyl” means a bi-cyclic hydrocarbon ring system having 25 from 8 to 14 carbon atoms and at least one saturated cyclic alkyl ring. Representative (C₈-C₁₄)bicycloalkyls include -indanyl, -1,2,3,4-tetrahydronaphthyl, -5,6,7,8-tetrahydronaphthyl, -perhydronaphthyl and the like.

“(C₈-C₁₄)tricycloalkyl” means a tri-cyclic hydrocarbon ring system having from 8 to 14 carbon atoms and at least one saturated ring. Representative (C₈- 30 C₁₄)tricycloalkyls include -pyrenyl, -1,2,3,4-tetrahydroanthracenyl, -perhydroanthracenyl, -aceanthrene, -1,2,3,4-tetrahydropenanthrenyl, -5,6,7,8-tetrahydrophenanthrenyl,

-perhydrophenanthrenyl and the like.

“(C₅-C₁₀)cycloalkenyl” means a cyclic non-aromatic hydrocarbon having at least one carbon-carbon double bond in the cyclic system and from 5 to 10 carbon atoms.

Representative (C₅-C₁₀)cycloalkenyls include -cyclopentenyl, -cyclopentadienyl,

- 5 -cyclohexenyl, -cyclohexadienyl, -cycloheptenyl, -cycloheptadienyl, -cycloheptatrienyl, -cyclooctenyl, -cyclooctadienyl, -cyclooctatrienyl, -cyclooctatetraenyl, -cyclononenyl -cyclononadienyl, -cyclodecenyl, -cyclodecadienyl and the like.

“(C₅-C₈)cycloalkenyl” means a cyclic non-aromatic hydrocarbon having at least one carbon-carbon double bond in the cyclic system and from 5 to 8 carbon atoms.

- 10 Representative (C₅-C₈)cycloalkenyls include -cyclopentenyl, -cyclopentadienyl, -cyclohexenyl, -cyclohexadienyl, -cycloheptenyl, -cycloheptadienyl, -cycloheptatrienyl, -cyclooctenyl, -cyclooctadienyl, -cyclooctatrienyl, -cyclooctatetraenyl and the like.

“(C₈-C₁₄)bicycloalkenyl” means a bi-cyclic hydrocarbon ring system having at least one carbon-carbon double bond in each ring and from 8 to 14 carbon atoms.

- 15 Representative -(C₈-C₁₄)bicycloalkenyls include -indenyl, -pentalenyl, -naphthalenyl, -azulenyl, -heptalenyl, -1,2,7,8-tetrahydronaphthalenyl and the like.

“(C₈-C₁₄)tricycloalkenyl” means a tri-cyclic hydrocarbon ring system having at least one carbon-carbon double bond in each ring and from 8 to 14 carbon atoms.

Representative -(C₈-C₁₄)tricycloalkenyls include -anthracenyl, -phenanthrenyl,

- 20 -phenalenyl, -acenaphthalenyl, *as*-indacenyl, *s*-indacenyl and the like.

“(C₃-C₇)heterocycle” or “-(C₃-C₇)heterocyclo” means a 3- to 7-membered monocyclic heterocyclic ring which is either saturated, unsaturated non-aromatic, or aromatic.

A 3-membered -(C₃-C₇)heterocycle can contain up to 3 heteroatoms, and a 4- to 7-membered -(C₃-C₇)heterocycle can contain up to 4 heteroatoms. Each heteroatom is independently

- 25 selected from nitrogen, which can be quaternized; oxygen; and sulfur, including sulfoxide and sulfone. The -(C₃-C₇)heterocycle can be attached via a nitrogen, sulfur, or carbon atom.

Representative -(C₃-C₇)heterocycles include pyridyl, furyl, thiophenyl, pyrrolyl, oxazolyl, imidazolyl, thiazolyl, thiadiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, morpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl,

- 30 piperazinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, tetrahydrofuranyl,

tetrahydropyranyl, tetrahydropyrindinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl and the like.

"-(C₃-C₅)heterocycle" or "-(C₃-C₅)heterocyclo" means a 3- to 5-membered monocyclic heterocyclic ring which is either saturated, unsaturated non-aromatic, or aromatic.

- 5 A 3-membered -(C₃-C₇)heterocycle can contain up to 3 heteroatoms, and a 4- to 5-membered -(C₃-C₅)heterocycle can contain up to 4 heteroatoms. Each heteroatom is independently selected from nitrogen, which can be quaternized; oxygen; and sulfur, including sulfoxide and sulfone. The -(C₃-C₅)heterocycle can be attached via a nitrogen, sulfur, or carbon atom. Representative -(C₃-C₅)heterocycles include furyl, thiophenyl, pyrrolyl, oxazolyl, imidazolyl, thiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, triazinyl, pyrrolidinonyl, pyrrolidinyl, hydantoinyl, oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydrothiophenyl and the like.

- "-(C₇-C₁₀)bicycloheterocycle" or "-(C₇-C₁₀)bicycloheterocyclo" means a 7- to 10-membered bicyclic, heterocyclic ring which is either saturated, unsaturated non-aromatic, or aromatic. A -(C₇-C₁₀)bicycloheterocycle contains from 1 to 4 heteroatoms independently selected from nitrogen, which can be quaternized; oxygen; and sulfur, including sulfoxide and sulfone. The (C₇-C₁₀)bicycloheterocycle can be attached via a nitrogen, sulfur, or carbon atom. Representative -(C₇-C₁₀)bicycloheterocycles include -quinolinyl, -isoquinolinyl, -chromonyl, -coumarinyl, -indolyl, -indoliziny, -benzo[b]furanyl, -benzo[b]thiophenyl, -indazolyl, -purinyl, -4H-quinoliziny, -isoquinolyl, -quinolyl, -phthalazinyl, -naphthyridinyl, -carbazolyl, - β -carbolinyl and the like.

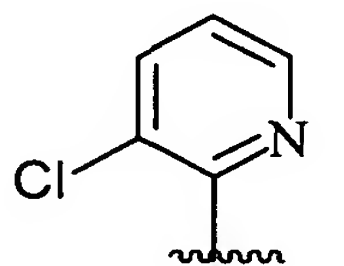
"-(C₁₄)aryl" means a 14-membered aromatic carbocyclic moiety such as -anthryl or -phenanthryl.

- "-(C₅-C₁₀)heteroaryl" means an aromatic heterocycle ring of 5 to 10 members, including both mono- and bicyclic ring systems, wherein at least one carbon atom of one or both of the rings is replaced with a heteroatom independently selected from nitrogen, oxygen and sulfur. One or both of the -(C₅-C₁₀)heteroaryl's rings contain at least one carbon atom. Representative (C₅-C₁₀)heteroaryls include pyridyl, furyl, benzofuranyl, thiophenyl, benzothiophenyl, quinolinyl, pyrrolyl, indolyl, oxazolyl, benzoxazolyl, imidazolyl, benzimidazolyl, thiazolyl, benzothiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiadiazolyl, triazinyl, cinnolinyl, phthalazinyl, and quinazolinyl.

"-Halogen" or "-Halo" means -F, -Cl, -Br or -I.

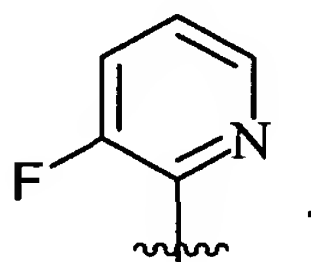
The phrase "2-(3-chloropyridyl)" means

5



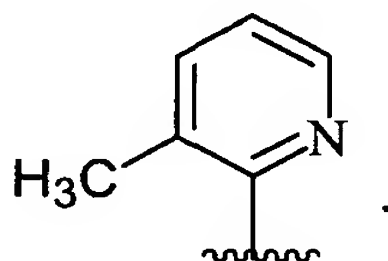
The phrase "2-(3-fluoropyridyl)" means

10



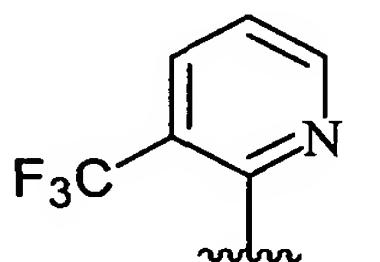
The phrase "2-(3-methylpyridyl)" means

15



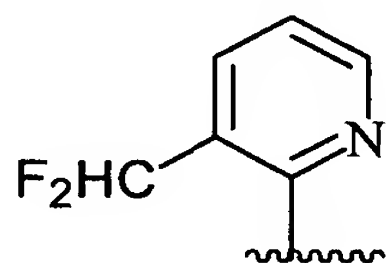
The phrase "2-(3-CF₃-methylpyridyl)" means

20



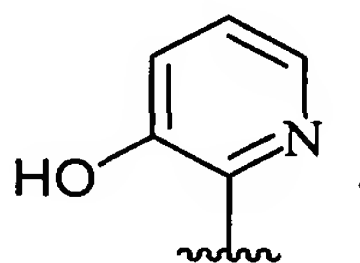
The phrase "2-(3-CHF₂-methylpyridyl)" means

25

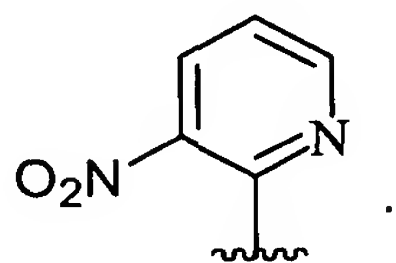


The phrase "2-(3-hydroxypyridyl)" means

30

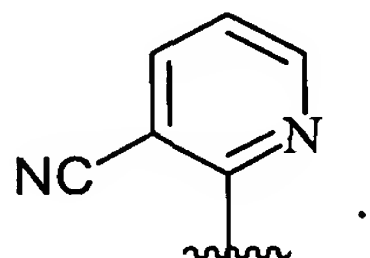


The phrase “2-(3-nitropyridyl)” means



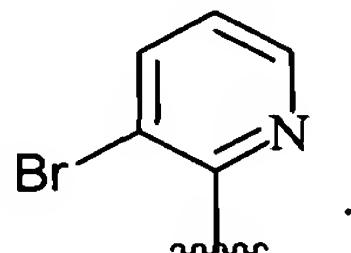
5

The phrase “2-(3-cyanopyridyl)” means



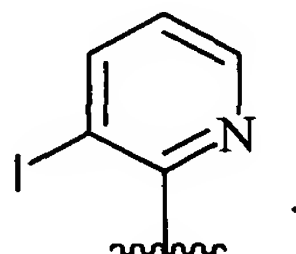
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The phrase “2-(3-bromopyridyl)” means



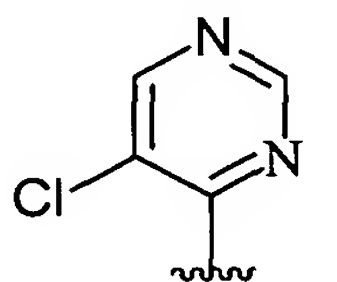
15

The phrase “2-(3-iodopyridyl)” means



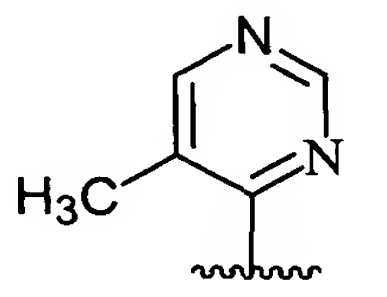
20

The phrase “4-(5-chloropyrimidinyl)” means



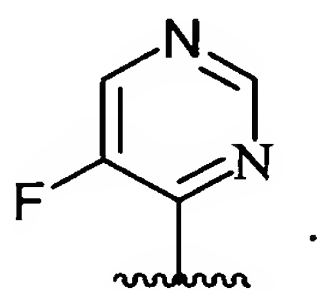
25

The phrase “4-(5-methylpyrimidinyl)” means



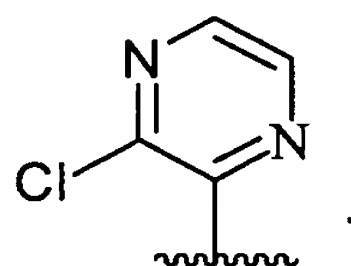
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The phrase “4-(5-fluoropyrimidinyl)” means



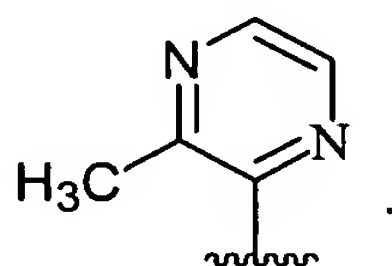
5

The phrase “2-(3-chloropyrazinyl)” means



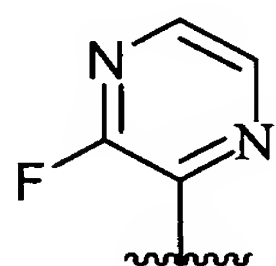
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The phrase “2-(3-methylpyrazinyl)” means



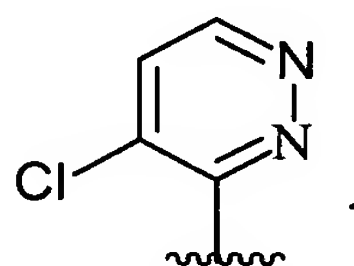
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The phrase “2-(3-fluoropyrazinyl)” means



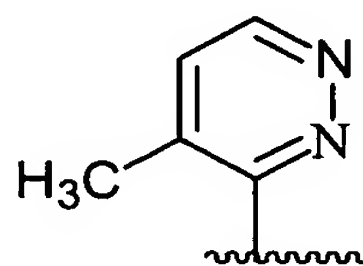
20

The phrase “3-(4-chloropyridazinyl)” means



25

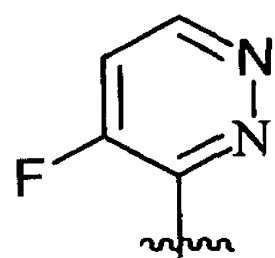
The phrase “3-(4-methylpyridazinyl)” means



30

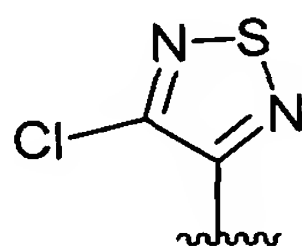
The phrase “3-(4-fluoropyridazinyl)” means

5



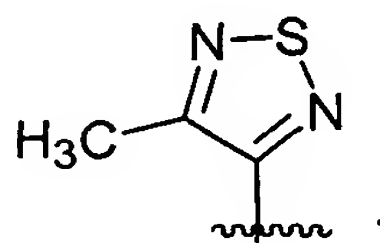
The phrase “5-(4-chlorothiadiazolyl)” means

10



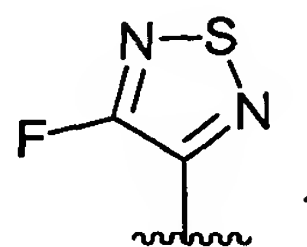
The phrase “5-(4-methylthiadiazolyl)” means

15



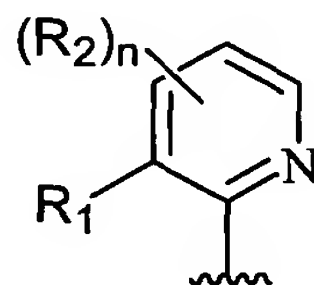
The phrase “5-(4-fluorothiadiazolyl)” means

20



The phrase “pyridyl group” in connection with the Cyanoiminopiperazine Compounds of formula (I), (Ia), and (Ib) means

25



wherein R₁, R₂, and n are defined above for the Cyanoiminopiperazine Compounds of formula (I), (Ia), and (Ib).

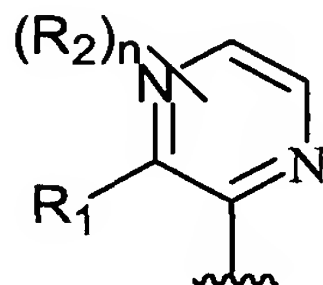
30

The phrase “pyridyl group” in connection with the Cyanoiminopiperazine
Compounds of formula (Ic) means



wherein R_{11} , R_{12} , and q are defined above for the Cyanoiminopiperazine Compounds of
formula (Ic).

The phrase “pyrazinyl group” in connection with the Cyanoiminopiperazine
10 Compounds of formula (II) means



15 wherein R_1 , R_2 , and n are defined above for the Cyanoiminopiperazine Compounds of
formula (II).

The phrase “pyrazinyl group” in connection with the Cyanoiminopiperazine
Compounds of formula (IIa) means



wherein R_1 , R_2 , and q are defined above for the Cyanoiminopiperazine Compounds of
formula (IIa).

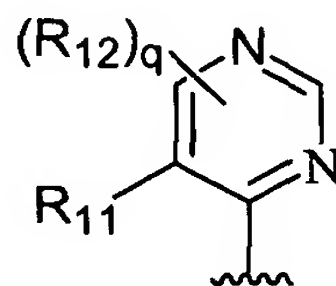
25 The phrase “pyrimidinyl group” in connection with the Cyanoiminopiperazine
Compounds of formula (III), (IIIa), and (IIIb) means



wherein R_1 , R_2 , and n are defined above for the Cyanoiminopiperazine Compounds of formula (III), (IIIa), and (IIIb).

The phrase “pyrimidinyl group” in connection with the Cyanoiminopiperazine Compounds of formula (IIIc) means

5

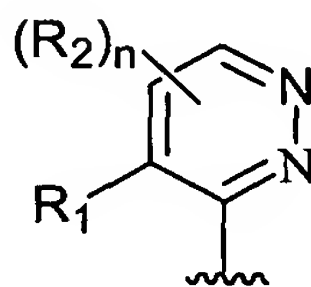


wherein R_{11} , R_{12} , and q are defined above for the Cyanoiminopiperazine Compounds of formula (IIIc).

10

The phrase “pyridizanyl group” in connection with the Cyanoiminopiperazine Compounds of formula (IV) means

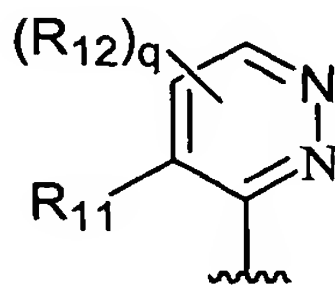
15



wherein R_1 , R_2 , and n are defined above for the Cyanoiminopiperazine Compounds of formula (IV).

The phrase “pyridizanyl group” in connection with the Cyanoiminopiperazine Compounds of formula (IVa) means

20

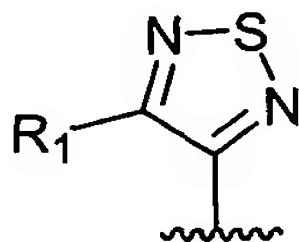


wherein R_{11} , R_{12} , and q are defined above for the Cyanoiminopiperazine Compounds of formula (IVa).

25

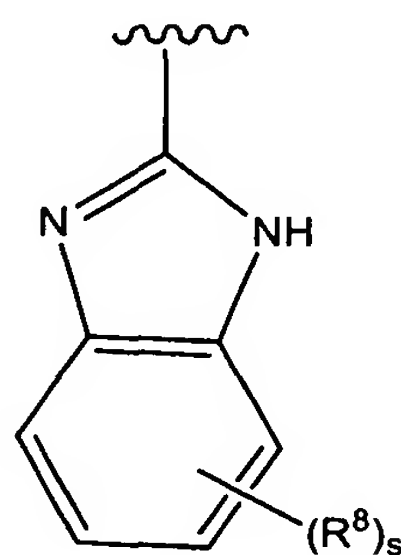
The phrase “thiadiazolyl group” means

30



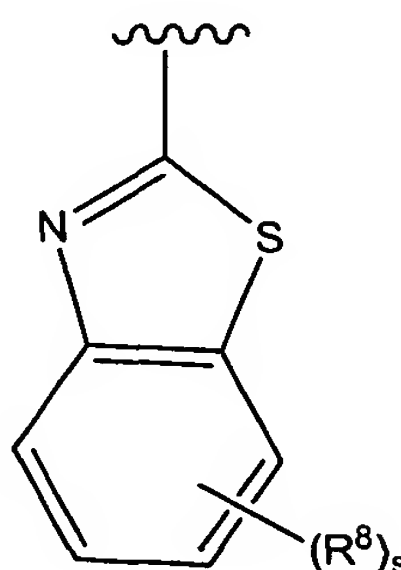
wherein R_1 is defined above for the Cyanoiminopiperazine Compounds of formula (V).

The phrase “benzothiazolyl group” means



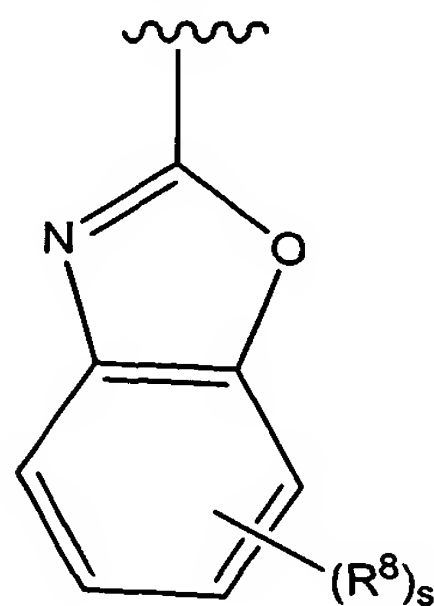
10 wherein R^8 and s are defined above for the Cyanoiminopiperazine Compounds of formulas (VI) and (VII).

The phrase “benzimidazolyl group” means



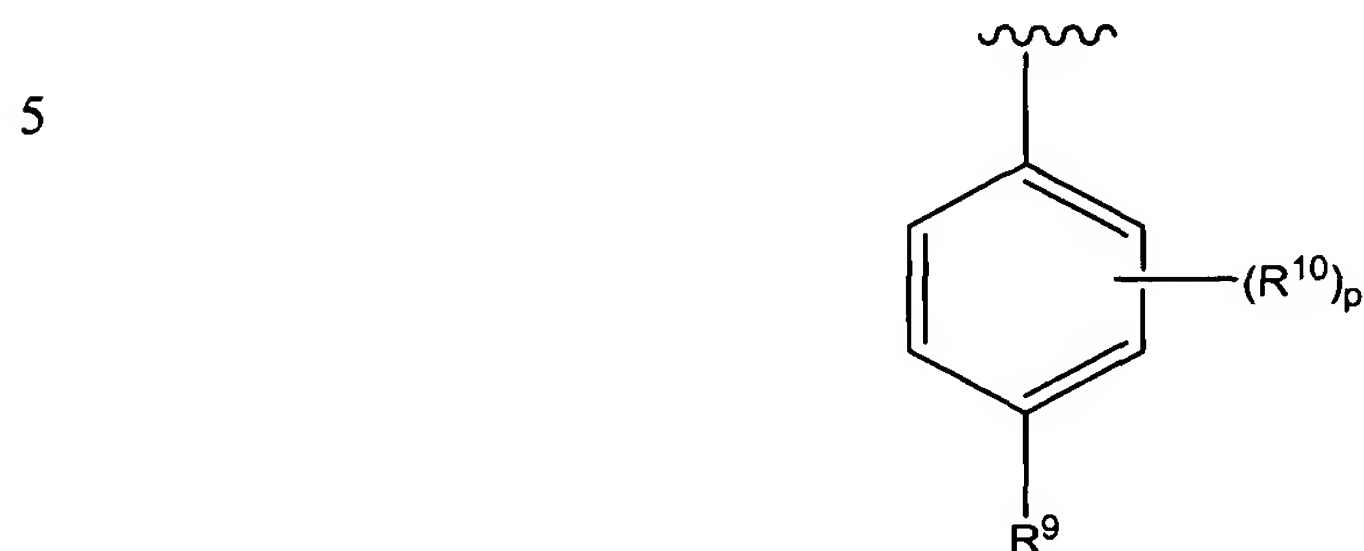
20 wherein R^8 and s are defined above for the Cyanoiminopiperazine Compounds of formulas (VI) and (VII).

The phrase “benzooxazolyl group” means



wherein R^8 and s are defined above for the Cyanoiminopiperazine Compounds of formulas (VI) and (VII).

The phrase “ (R^9) -phenyl group” means



The phrase “phenethyl group” means an ethylene group attached to a terminal Ar_2 group, wherein one or each of two hydrogens of the ethylene group can optionally be substituted with an R^4 group. A phenethyl group is depicted below



wherein R^4 , Ar_2 , and t are defined above for the Cyanoiminopiperazine Compounds of formula (VI).

The phrase “phenpropyl group” an n-propylene group attached to a terminal Ar_2 group, wherein one or each of two hydrogens of the n-propylene group can optionally be substituted with an R^4 group. A phenpropyl group is depicted below



wherein R^4 , Ar_2 , and t are defined above for the Cyanoiminopiperazine Compounds of formula (VII).

The term "animal," includes, but is not limited to, a cow, monkey, horse, sheep, pig, chicken, turkey, quail, cat, dog, mouse, rat, rabbit, guinea pig and human.

The phrase "pharmaceutically acceptable salt," as used herein, is a salt formed from an acid and a basic nitrogen group of one of the Cyanoiminopiperazine Compounds.

5 Illustrative salts include, but are not limited, to sulfate, citrate, acetate, oxalate, chloride, bromide, iodide, nitrate, bisulfate, phosphate, acid phosphate, isonicotinate, lactate, salicylate, acid citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, *p*-toluenesulfonate, and pamoate (*i.e.*,
10 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)) salts. The term "pharmaceutically acceptable salt" also refers to a salt prepared from a Cyanoiminopiperazine Compound having an acidic functional group, such as a carboxylic acid functional group, and a pharmaceutically acceptable inorganic or organic base. Suitable bases include, but are not limited to, hydroxides of alkali metals such as sodium, potassium, and lithium; hydroxides of alkaline
15 earth metal such as calcium and magnesium; hydroxides of other metals, such as aluminum and zinc; ammonia, and organic amines, such as unsubstituted or hydroxy-substituted mono-, di-, or trialkylamines; dicyclohexylamine; tributyl amine; pyridine; N-methyl,N-ethylamine; diethylamine; triethylamine; mono-, bis-, or tris-(2-hydroxy-lower alkyl amines), such as mono-, bis-, or tris-(2-hydroxyethyl)amine, 2-hydroxy-tert-butylamine, or
20 tris-(hydroxymethyl)methylamine, N, N,-di-lower alkyl-N-(hydroxy lower alkyl)-amines, such as N,N,-dimethyl-N-(2-hydroxyethyl)amine, or tri-(2-hydroxyethyl)amine; N-methyl-D-glucamine; and amino acids such as arginine, lysine, and the like.

When a first group is "substituted with one or more" second groups, each of one or more of the first group's hydrogen atoms is replaced with a second group. In one
25 embodiment, each carbon atom of a first group is independently substituted with one or two second groups. In another embodiment, each carbon atom of a first group is independently substituted with only one second group.

The term "UI" means urinary incontinence.

The term "IBD" means inflammatory-bowel disease.

30 The term "IBS" means irritable-bowel syndrome.

The term "DIEA" means diisopropylethylamine.

The term "DMSO" means dimethyl sulfoxide.

The term "DMF" means dimethyl formamide.

The term "DCM" means dichloromethane.

The phrase "treatment of" and "treating" includes the amelioration or

5 cessation of a Condition or a symptom thereof.

The term “DMF” means dimethyl formamide.

The term “DCM” means dichloromethane.

The phrase "treatment of" and "treating" includes the amelioration or
5 cessation of a Condition or a symptom thereof.

The phrase "prevention of" and "preventing" includes the avoidance of the
onset of a Condition or a symptom thereof.

The term “DCM” means dichloromethane.

The phrase "treatment of" and "treating" includes the amelioration or
5 cessation of a Condition or a symptom thereof.

The phrase "treatment of" and "treating" includes the amelioration or
5 cessation of a Condition or a symptom thereof.

The phrase "prevention of" and "preventing" includes the avoidance of the
onset of a Condition or a symptom thereof.

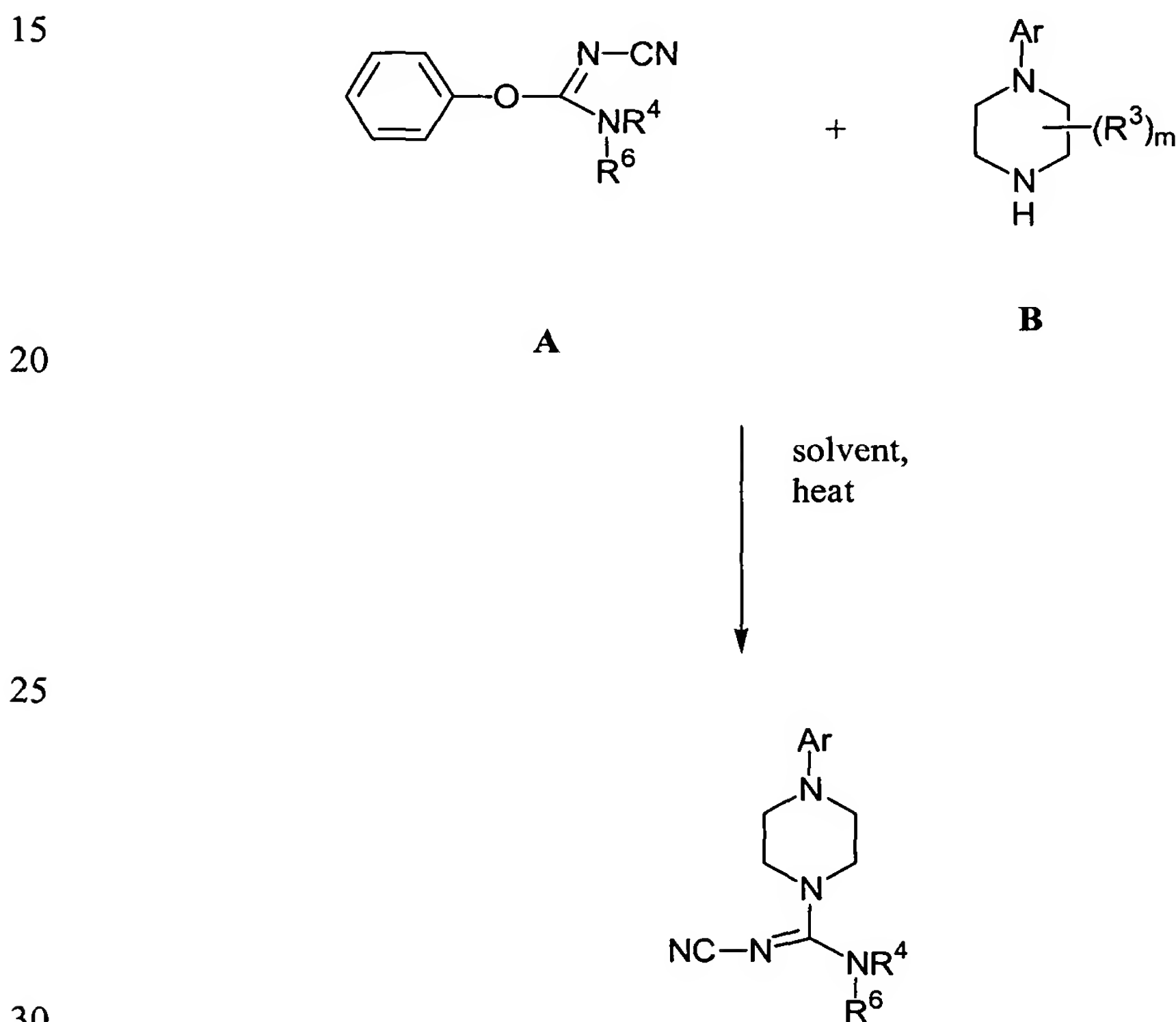
5 cessation of a Condition or a symptom thereof.

The phrase "prevention of" and "preventing" includes the avoidance of the onset of a Condition or a symptom thereof.

4.18 METHODS FOR MAKING THE CYANOIMINOPIPERAZINE COMPOUNDS

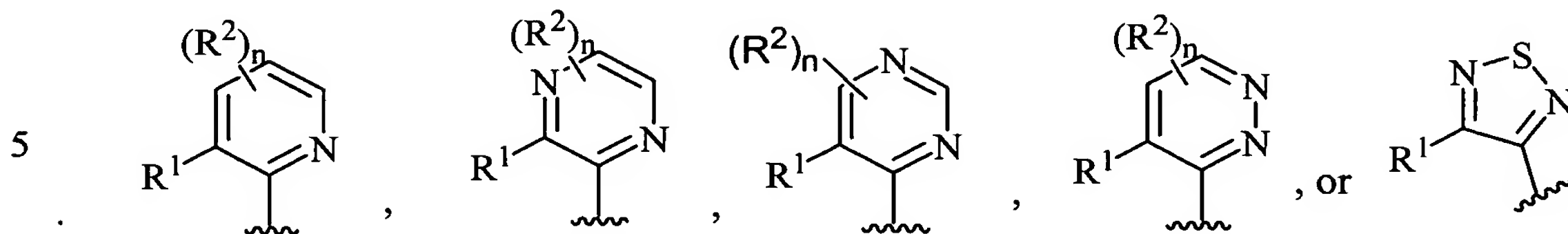
10 The Cyanoiminopiperazine Compounds can be made using conventional organic synthesis or by the following illustrative methods shown in the schemes below. The Cyanoiminopiperazine Compounds wherein A is NR⁴ can be obtained by the following illustrative methods shown below in Scheme A:

10 The Cyanoiminopiperazine Compounds can be made using conventional organic synthesis or by the following illustrative methods shown in the schemes below. The Cyanoiminopiperazine Compounds wherein A is NR⁴ can be obtained by the following illustrative methods shown below in Scheme A:



Scheme A

wherein R^3 , R^4 , R^6 , and m are defined above for the Cyanoiminopiperazine Compounds and Ar is:



wherein R^1 , R^2 and n are defined above.

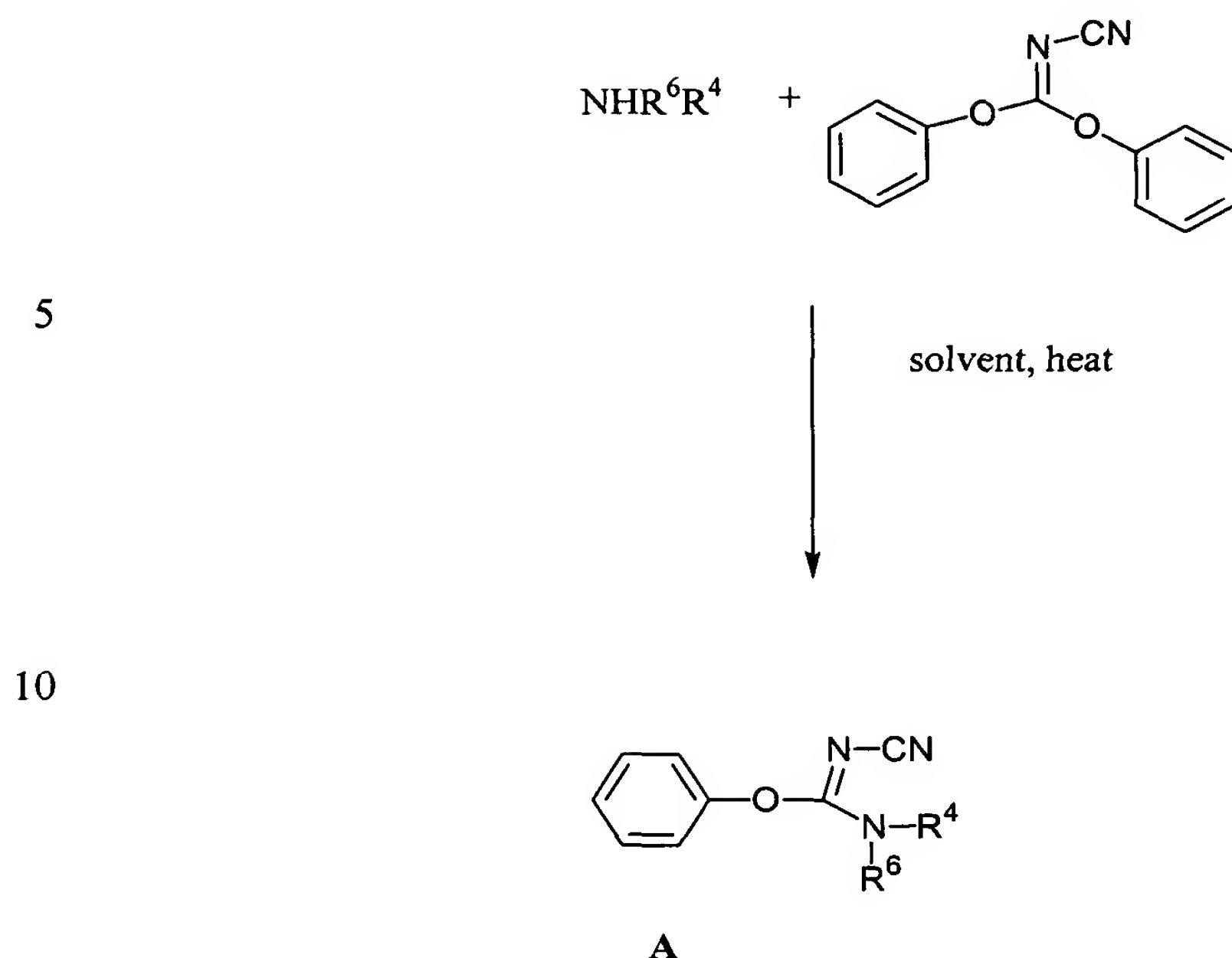
A compound of formula **A** is reacted with a compound of formula **B** in an
 10 aprotic organic solvent such as diethyl ether, di-n-propyl ether, tetrahydrofuran, methylene
 chloride, or toluene at a temperature ranging from about room temperature to about the reflux
 temperature of the solvent for a period of about 0.5 h to about 24 h to provide a
 Cyanoiminopiperazine Compound wherein A is NR^4 . In one embodiment, the aprotic organic
 solvent is di-n-propyl ether. In another embodiment, a reaction mixture of di-n-propyl ether,
 15 a compound of formula **A** and a compound of formula **B** is heated at a temperature of about
 70° to about 80° C. In another embodiment, the reaction mixture of di-n-propyl ether, a
 compound of formula **A** and a compound of formula **B** is heated at a temperature of about at
 75°C for about 12 h.

Compounds of formula **A** can be obtained as shown below in Scheme B:

20

25

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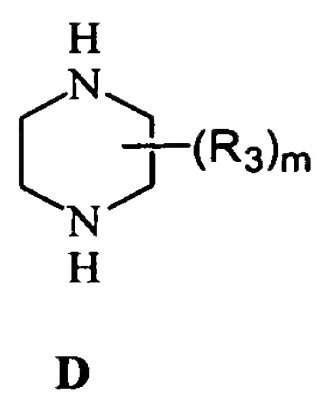


15 **Scheme B**

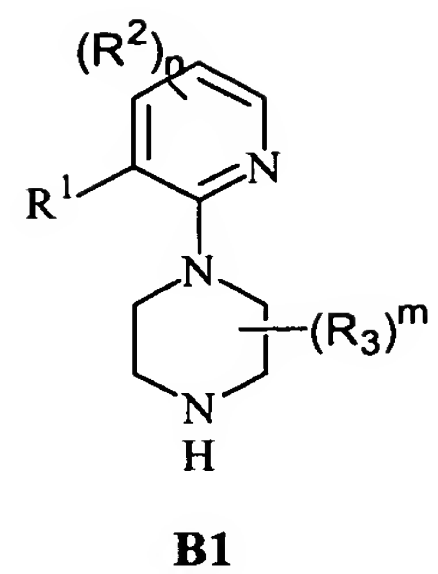
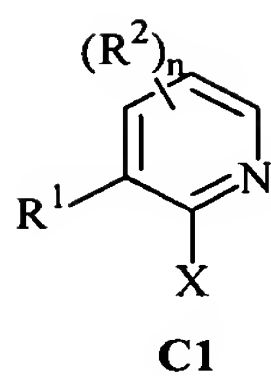
An amine of formula NHR^6R^4 , wherein R^4 and R^6 are defined above, is reacted with diphenylcyanocarbonimidate (commercially available from Sigma-Aldrich, St. Louis, MO (www.sigma-aldrich.com)) in an aprotic solvent such as diethyl ether, di-n-propyl ether, tetrahydrofuran, methylene chloride, or toluene to provide the compound of formula A. In one embodiment, the aprotic solvent is DCM and the reaction mixture of NHR^6R^4 and diphenylcyanocarbonimidate is allowed to react at about room temperature. In another embodiment, the aprotic solvent is toluene and the reaction mixture of NHR^6R^4 and diphenylcyanocarbonimidate is allowed to react at about 110°C . The NHR^6R^4 and diphenylcyanocarbonimidate is typically allowed to react for a period of about 0.5 h to about 24 h. Typically the compound of formula A is used without further purification.

Compounds of formula B can be obtained as shown below in Scheme C:

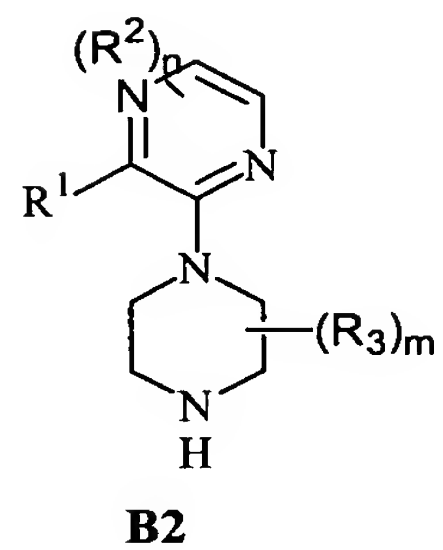
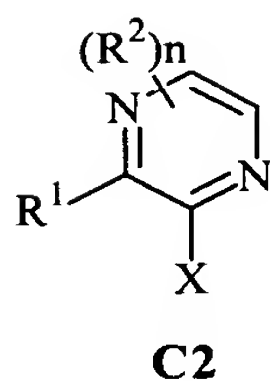
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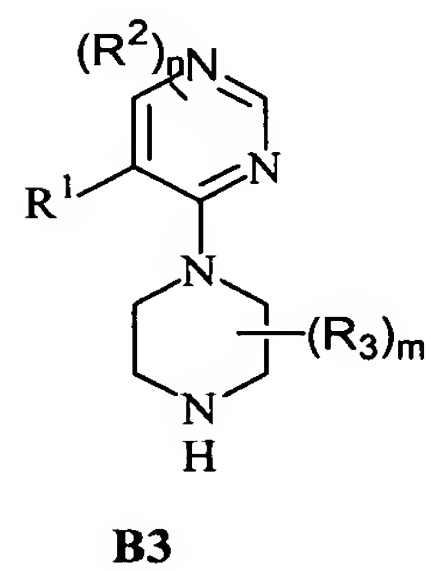
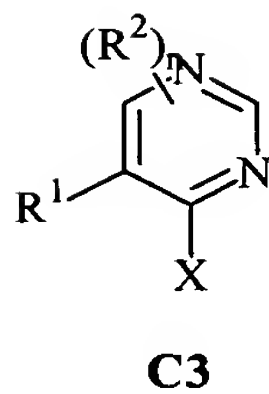
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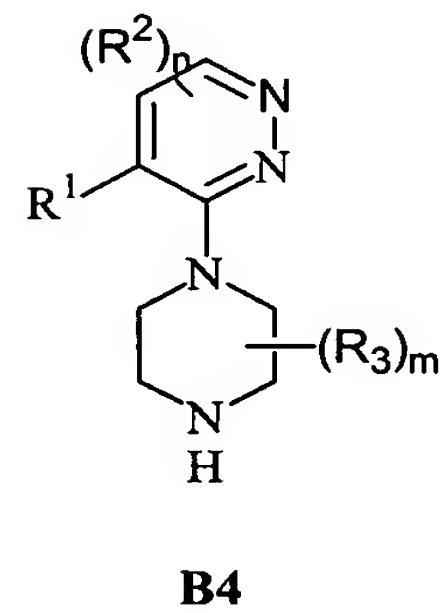
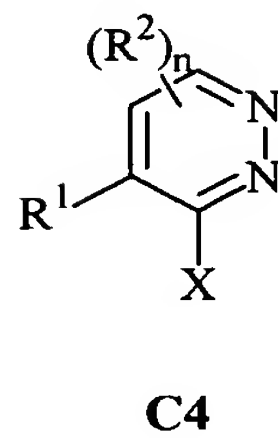
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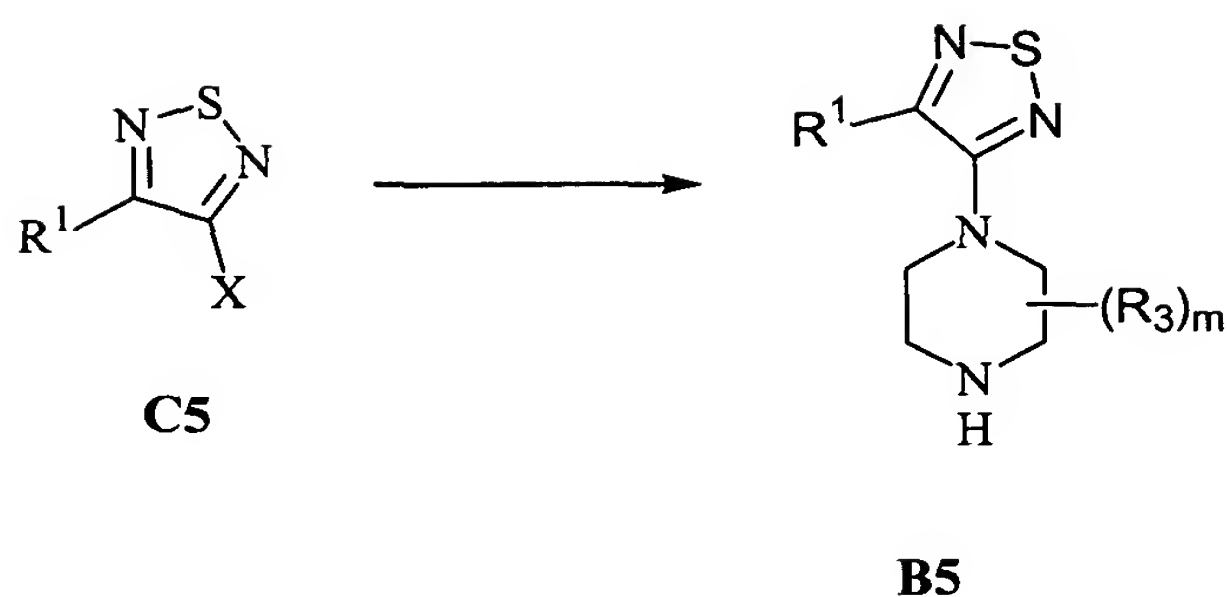


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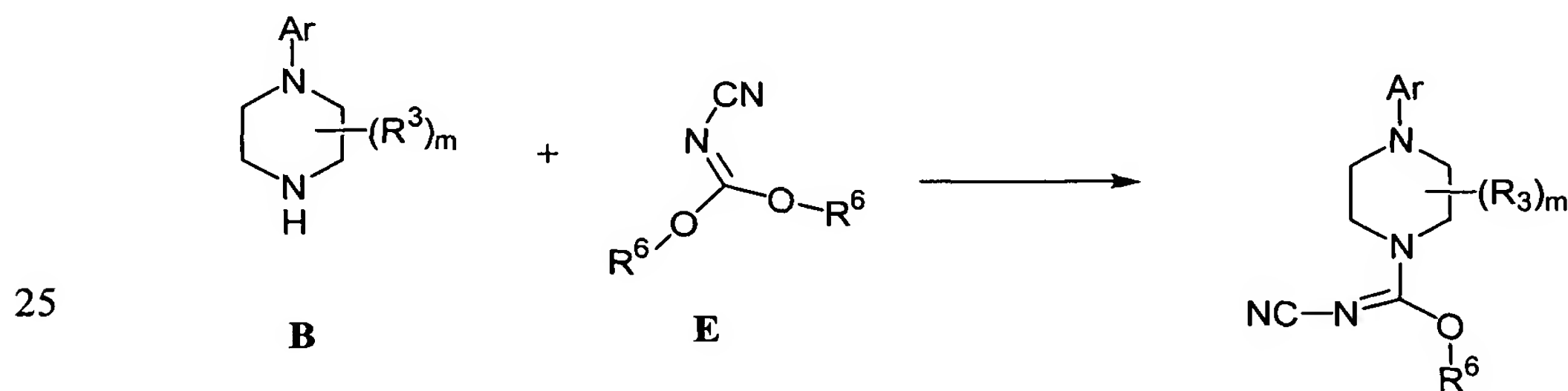
Scheme C

wherein R^1 , R^2 , R^3 , m , and n are defined above and X is a halogen. In one embodiment, X is
 10 bromide, chloride or iodide.

A compound of formula **C1-C5** is reacted with a compound of formula **D** in an aprotic solvent in the presence of DIEA or triethylamine, optionally with heating, to provide compound **B**. Compound **B** is isolated from the reaction mixture and purified. In one embodiment, the reaction is purified using column chromatography or recrystallization.

15 Compounds of formula **C1-C5** and **D** are commercially available or can be prepared by methods well known to those skilled in the art. The compound of formula **D** wherein m is 0 is commercially available from Sigma-Aldrich, St. Louis, MO (www.sigma-aldrich.com).

The Cyanoiminopiperazine Compounds wherein A is $-O-$ can be obtained as
 20 shown below in Scheme **D**.



Scheme D

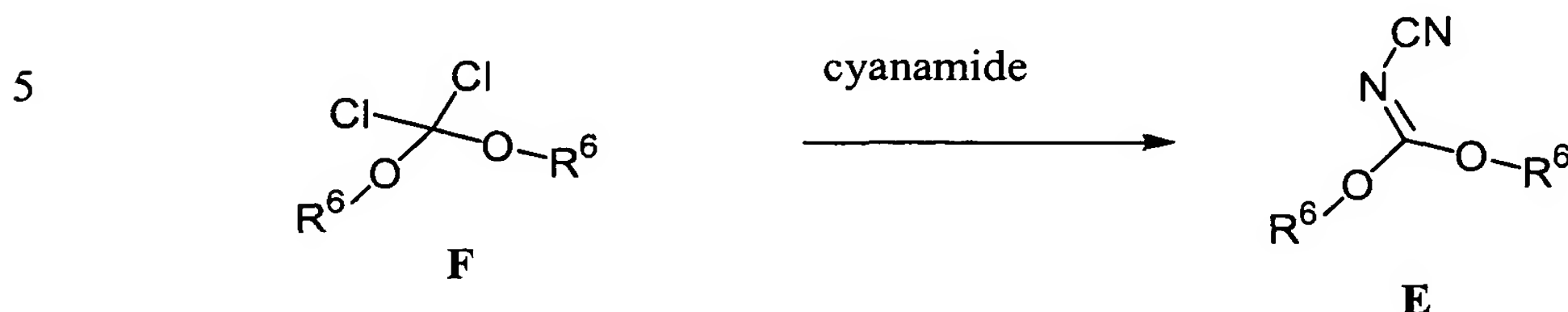
wherein R^3 , R^6 , m , and Ar are defined above for the Cyanoiminopiperazine Compounds.

30 A compound of formula **B** is reacted with a compound of formula **E** to provide the Cyanoiminopiperazine Compounds wherein A is $-O-$. Representative procedures for

reacting a compound of formula **B** with a compound of formula **E** are provided in T.D.

Aicher et al., *J. Med. Chem.* 43(2):236-49 (2000) and German Patent No. 3336409.

The compound of formula **E** can be obtained as shown below in Scheme E.

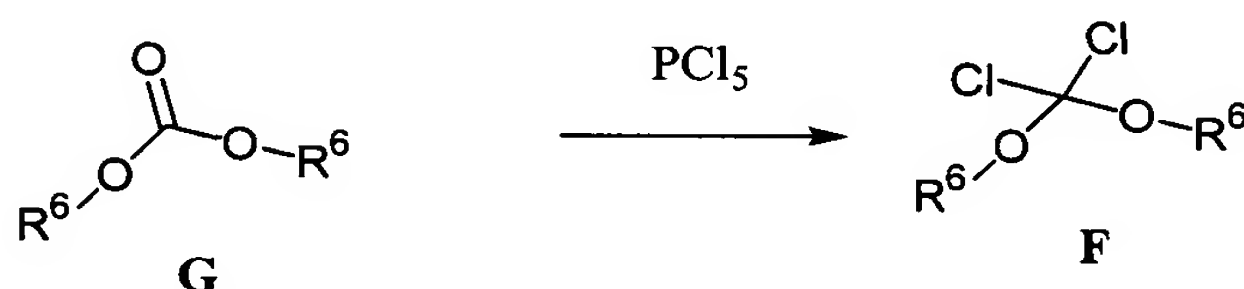


Scheme E

10 wherein R^6 is defined above.

The compound of formula **E** can be obtained by reacting a compound of formula **F** with cyanamide. Representative procedures for obtaining a compound of formula **E** from a compound of formula **F** are provided in R.L. Webb et al., *J. Heterocycl. Chem.* 19(5):1205-1206 (1982) and U.S. Patent No. 4,285,878 to Labaw et al.

15 The compound of formula **F** can be obtained as shown below in Scheme F.



Scheme F

20 wherein R^6 is defined above.

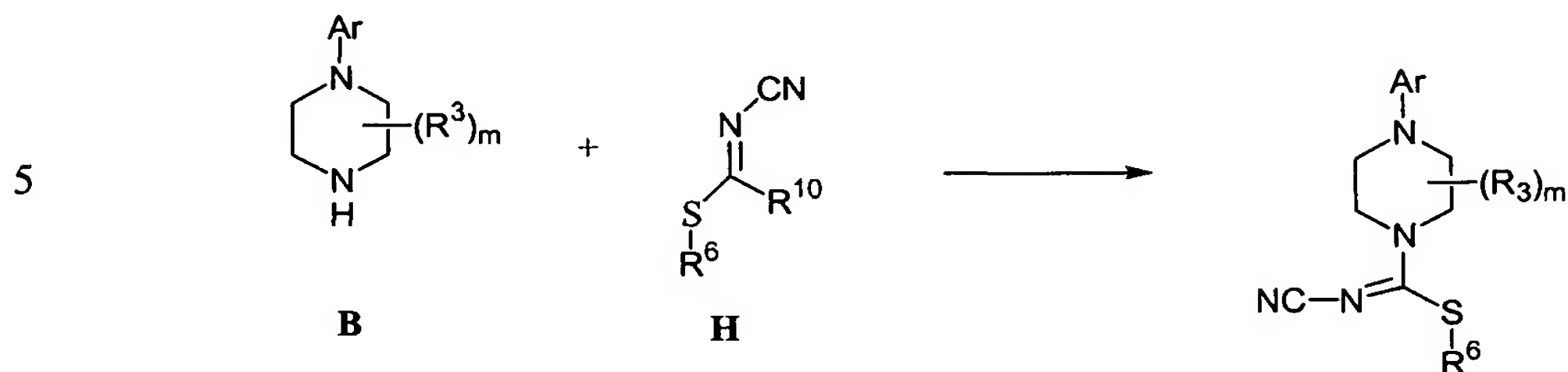
The compound of formula **F** can be obtained by reacting a compound of formula **G** with PCl_5 . A representative procedure for obtaining a compound of formula **F** from a compound of formula **G** is provided in R.L. Webb et al., *J. Heterocycl. Chem.*

25 19(5):1205-1206 (1982).

The compound of formula **G** can be obtained by reacting a compound of formula $\text{R}^6\text{-OH}$ with COCl_2 , triphosgene, or CO and a Pd catalyst as described in U.S. Patent No. 6,175,017 to H. Buyschi et al.; A. Gode et al., *Chemistry-A European Journal* 6(19):3522-30 (2000); or H. Yasuda et al., *Organometallics*, 21(6):1216-20 (2002),

30 respectively. Compounds of formula $\text{R}^6\text{-OH}$ are commercially available or can be prepared by methods well known to those skilled in the art.

The Cyanoiminopiperazine Compounds wherein A is -S- can be obtained as shown below in Scheme G.

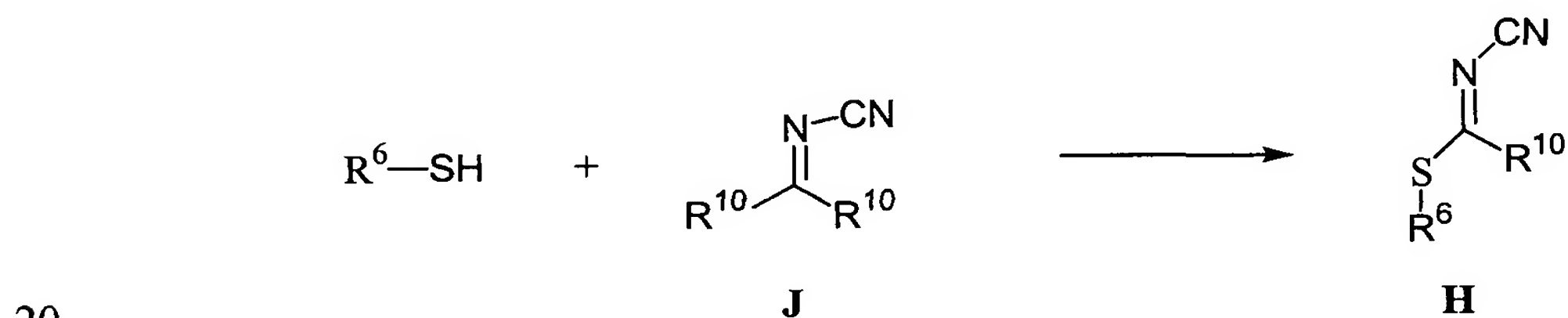


Scheme G

10 wherein R^6 , R^3 , m , and Ar are defined above and R^{10} is $-SCH_3$ or $-O-C_6H_5$.

A compound of formula **B** is reacted with a compound of formula **H** to provide the Cyanoiminopiperazine Compounds wherein A is -S-. Representative procedures for reacting a compound of formula **B** with a compound of formula **H** are provided in T.D. Aicher et al., *J. Med. Chem.* 43(2):236-49 (2000) and Ger. Patent No. 3336409.

15 The compound of formula **H** can be obtained as shown below in Scheme H.

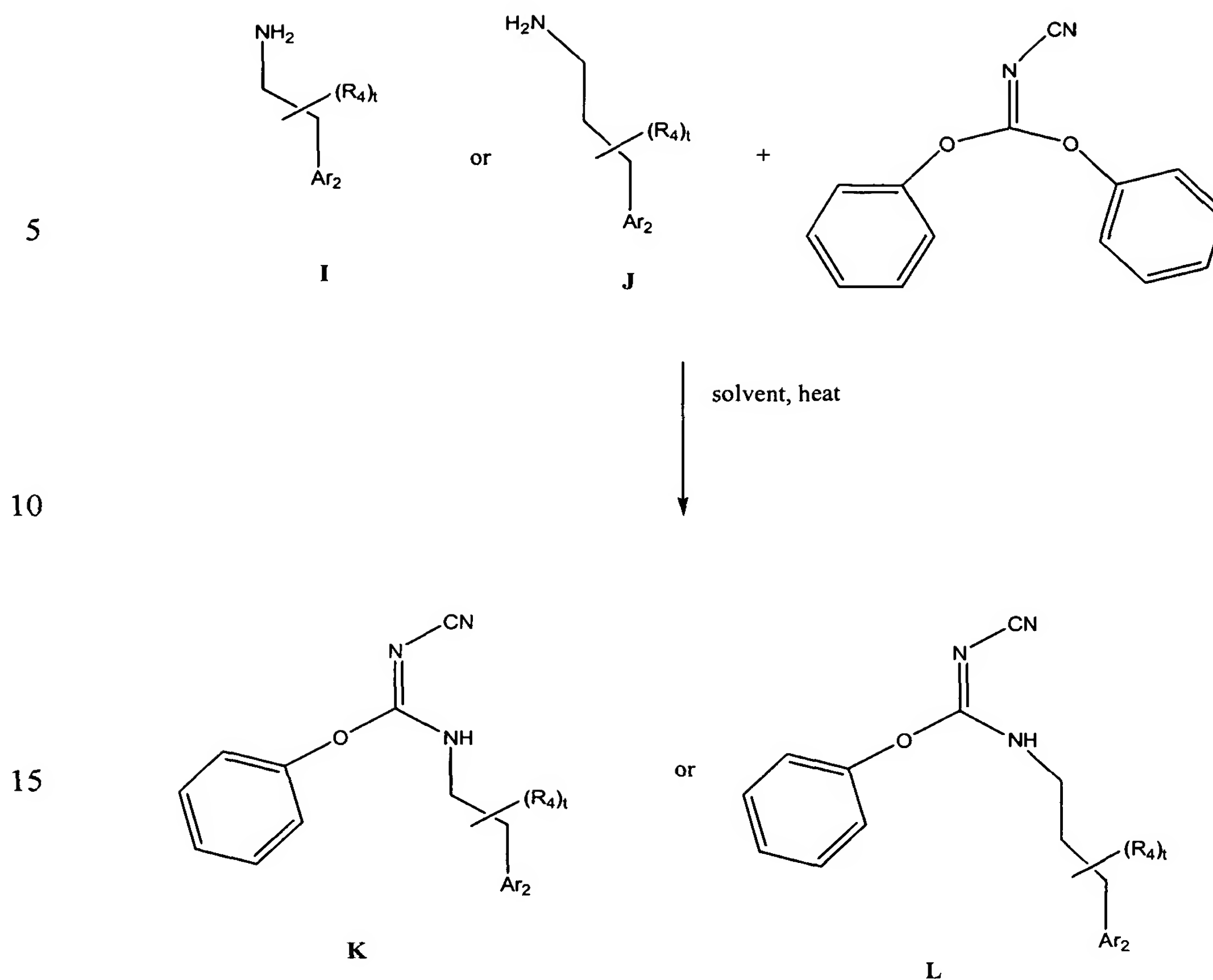


Scheme H

wherein R^6 and R^{10} are defined above.

A thiol of formula R^6SH is reacted with a compound of formula **J** to provide the compound of formula **H**. Representative procedures for obtaining compounds of formula **J** and for obtaining the compound of formula **H** by reacting a thiol with a compound of formula **J** are provided in R.L. Webb et al., *J. Heterocycl. Chem.*, 24(1):275-78 (1987); I. Reid et al., *Liebigs Ann. Chem.* 6:599-601 (1988); and L.S. Wittenbrook et al., *J. Heterocycl. Chem.* 12(1):37-42 (1975). Compounds of formula R^6-SH are commercially available or can be prepared by methods well known to those skilled in the art.

30 The Cyanoiminopiperazine Compounds of formula VI and VII can be obtained as described below in Scheme I.



20 wherein Ar_2 , R_4 , and t are defined above.

Scheme I

An amine of formula I or an amine of formula J is reacted with diphenylcyanocarbonimidate (commercially available from Sigma-Aldrich, St. Louis, MO (www.sigma-aldrich.com)) in an aprotic solvent such as diethyl ether, di-n-propyl ether, tetrahydrofuran, methylene chloride, or toluene to provide the compound of formula K or a compound of formula L, respectively. In one embodiment, the aprotic solvent is DCM and the reaction mixture of the amine of formula I or the amine of formula J and diphenylcyanocarbonimidate is allowed to react at about room temperature. In another embodiment, the aprotic solvent is toluene and the reaction mixture of the amine of formula I or the amine of formula J and diphenylcyanocarbonimidate is allowed to react at about 110°C. The amine of formula I or the amine of formula J and diphenylcyanocarbonimidate is

25

30

typically allowed to react for a period of about 0.5 h to about 24 h. Typically the compound of formula **K** or the compound of formula **L** is used without further purification.

The compound of formula **K** or the compound of formula **L** is then reacted with a compound of formula **B**, obtained as described above in Scheme **B**, according to the
5 procedure described above in Scheme **A** to provide the Cyanoiminopiperazine Compound of formula (VI) or (VII) , respectively.

4.19 THERAPEUTIC USES OF THE CYANOIMINOPIPERAZINE COMPOUNDS

In accordance with the invention, the Cyanoiminopiperazine Compounds are
10 administered to an animal in need of treatment or prevention of pain, UI, an ulcer, IBD, IBS, an addictive disorder, Parkinson's disease, parkinsonism, anxiety, epilepsy, stroke, a seizure, a pruritic condition, psychosis, a cognitive disorder, a memory deficit, restricted brain function, Huntington's chorea, ALS, dementia, retinopathy, a muscle spasm, a migraine, vomiting, dyskinesia, or depression.

15 In one embodiment, an effective amount of a Cyanoiminopiperazine Compound can be used to treat or prevent any condition treatable or preventable by inhibiting VR1. Examples of conditions that are treatable or preventable by inhibiting VR1 include, but are not limited to, pain, UI, an ulcer, IBD, and IBS.

In another embodiment, an effective amount of a Cyanoiminopiperazine
20 Compound can be used to treat or prevent any condition treatable or preventable by inhibiting mGluR5. Examples of conditions that are treatable or preventable by inhibiting mGluR5 include, but are not limited to, pain, an addictive disorder, Parkinson's disease, parkinsonism, anxiety, a pruritic condition, and psychosis.

In another embodiment, an effective amount of a Cyanoiminopiperazine
25 Compound can be used to treat or prevent any condition treatable or preventable by inhibiting mGluR1. Examples of conditions that are treatable or preventable by inhibiting mGluR1 include, but are not limited to, pain, UI, an addictive disorder, Parkinson's disease, parkinsonism, anxiety, epilepsy, stroke, a seizure, a pruritic condition, psychosis, a cognitive disorder, a memory deficit, restricted brain function, Huntington's chorea, ALS, dementia,
30 retinopathy, a muscle spasm, a migraine, vomiting, dyskinesia, and depression.

The Cyanoiminopiperazine Compounds can be used to treat or prevent acute or chronic pain. Examples of pain treatable or preventable using the Cyanoiminopiperazine Compounds include, but are not limited to, cancer pain, central pain, labor pain, myocardial infarction pain, pancreatic pain, colic pain, post-operative pain, headache pain, muscle pain, 5 pain associated with intensive care, arthritic pain, neuropathic pain, and pain associated with a periodontal disease, including gingivitis and periodontitis.

The Cyanoiminopiperazine Compounds can also be used for inhibiting, preventing, or treating pain associated with inflammation or with an inflammatory disease in an animal.

The pain to be inhibited, treated or prevented may be associated with inflammation associated 10 with an inflammatory disease, which can arise where there is an inflammation of the body tissue, and which can be a local inflammatory response and/or a systemic inflammation. For example, the Cyanoiminopiperazine Compounds can be used to inhibit, treat, or prevent pain associated with inflammatory diseases including, but not limited to: organ transplant rejection; reoxygenation injury resulting from organ transplantation (see Grupp *et al.*, *J. Mol.* 15 *Cell Cardiol.* 31:297-303 (1999)) including, but not limited to, transplantation of the heart, lung, liver, or kidney; chronic inflammatory diseases of the joints, including arthritis, rheumatoid arthritis, osteoarthritis and bone diseases associated with increased bone resorption; inflammatory lung diseases, such as asthma, adult respiratory distress syndrome, and chronic obstructive airway disease; inflammatory diseases of the eye, including corneal 20 dystrophy, trachoma, onchocerciasis, uveitis, sympathetic ophthalmitis and endophthalmitis; chronic inflammatory diseases of the gum, including gingivitis and periodontitis; tuberculosis; leprosy; inflammatory diseases of the kidney, including uremic complications, glomerulonephritis and nephrosis; inflammatory diseases of the skin, including sclerodermatitis, psoriasis and eczema; inflammatory diseases of the central nervous system, 25 including chronic demyelinating diseases of the nervous system, multiple sclerosis, AIDS-related neurodegeneration and Alzheimer s disease, infectious meningitis, encephalomyelitis, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis and viral or autoimmune encephalitis; autoimmune diseases, including Type I and Type II diabetes mellitus; diabetic complications, including, but not limited to, diabetic cataract, glaucoma, 30 retinopathy, nephropathy (such as microalbuminuria and progressive diabetic nephropathy), polyneuropathy, mononeuropathies, autonomic neuropathy, gangrene of the feet,

atherosclerotic coronary arterial disease, peripheral arterial disease, nonketotic hyperglycemic-hyperosmolar coma, foot ulcers, joint problems, and a skin or mucous membrane complication (such as an infection, a shin spot, a candidal infection or necrobiosis lipoidica diabetorum); immune-complex vasculitis, and systemic lupus erythematosus (SLE); inflammatory diseases of the heart, such as cardiomyopathy, ischemic heart disease hypercholesterolemia, and atherosclerosis; as well as various other diseases that can have significant inflammatory components, including preeclampsia, chronic liver failure, brain and spinal cord trauma, and cancer. The Cyanoiminopiperazine Compounds can also be used for inhibiting, treating, or preventing pain associated with inflammatory disease that can, for example, be a systemic inflammation of the body, exemplified by gram-positive or gram negative shock, hemorrhagic or anaphylactic shock, or shock induced by cancer chemotherapy in response to pro-inflammatory cytokines, e.g., shock associated with pro-inflammatory cytokines. Such shock can be induced, e.g., by a chemotherapeutic agent that is administered as a treatment for cancer.

15 The Cyanoiminopiperazine Compounds can be used to treat or prevent UI. Examples of UI treatable or preventable using the Cyanoiminopiperazine Compounds include, but are not limited to, urge incontinence, stress incontinence, overflow incontinence, neurogenic incontinence, and total incontinence.

 The Cyanoiminopiperazine Compounds can be used to treat or prevent an ulcer. Examples of ulcers treatable or preventable using the Cyanoiminopiperazine Compounds include, but are not limited to, a duodenal ulcer, a gastric ulcer, a marginal ulcer, an esophageal ulcer, or a stress ulcer.

 The Cyanoiminopiperazine Compounds can be used to treat or prevent IBD, including Crohn's disease and ulcerative colitis.

25 The Cyanoiminopiperazine Compounds can be used to treat or prevent IBS. Examples of IBS treatable or preventable using the Cyanoiminopiperazine Compounds include, but are not limited to, spastic-colon-type IBS and constipation-predominant IBS.

 The Cyanoiminopiperazine Compounds can be used to treat or prevent an addictive disorder, including but not limited to, an eating disorder, an impulse-control disorder, an alcohol-related disorder, a nicotine-related disorder, an amphetamine-related disorder, a cannabis-related disorder, a cocaine-related disorder, an hallucinogen-related

disorder, an inhalant-related disorders, and an opioid-related disorder, all of which are further sub-classified as listed below.

Eating disorders include, but are not limited to, Bulimia Nervosa, Nonpurging Type; Bulimia Nervosa, Purging Type; Anorexia; and Eating Disorder not otherwise specified
5 (NOS).

Impulse control disorders include, but are not limited to, Intermittent Explosive Disorder, Kleptomania, Pyromania, Pathological Gambling, Trichotillomania, and Impulse Control Disorder not otherwise specified (NOS).

Alcohol-related disorders include, but are not limited to, Alcohol-Induced
10 Psychotic Disorder with delusions, Alcohol Abuse, Alcohol Intoxication, Alcohol Withdrawal, Alcohol Intoxication Delirium, Alcohol Withdrawal Delirium, Alcohol-Induced Persisting Dementia, Alcohol-Induced Persisting Amnestic Disorder, Alcohol Dependence, Alcohol-Induced Psychotic Disorder with hallucinations, Alcohol-Induced Mood Disorder, Alcohol-Induced Anxiety Disorder, Alcohol-Induced Sexual Dysfunction, Alcohol-Induced
15 Sleep Disorder, Alcohol-Related Disorder not otherwise specified (NOS), Alcohol Intoxication, and Alcohol Withdrawal.

Nicotine-related disorders include, but are not limited to, Nicotine Dependence, Nicotine Withdrawal, and Nicotine-Related Disorder not otherwise specified (NOS).

20 Amphetamine-related disorders include, but are not limited to, Amphetamine Dependence, Amphetamine Abuse, Amphetamine Intoxication, Amphetamine Withdrawal, Amphetamine Intoxication Delirium, Amphetamine-Induced Psychotic Disorder with delusions, Amphetamine-Induced Psychotic Disorders with hallucinations, Amphetamine-Induced Mood Disorder, Amphetamine-Induced Anxiety Disorder,
25 Amphetamine-Induced Sexual Dysfunction, Amphetamine-Induced Sleep Disorder, Amphetamine Related Disorder not otherwise specified (NOS), Amphetamine Intoxication, and Amphetamine Withdrawal.

Cannabis-related disorders include, but are not limited to, Cannabis Dependence, Cannabis Abuse, Cannabis Intoxication, Cannabis Intoxication Delirium,
30 Cannabis-Induced Psychotic Disorder with delusions, Cannabis-Induced Psychotic Disorder

with hallucinations, Cannabis-Induced Anxiety Disorder, Cannabis Related Disorder not otherwise specified (NOS), and Cannabis Intoxication.

Cocaine-related disorders include, but are not limited to, Cocaine Dependence, Cocaine Abuse, Cocaine Intoxication, Cocaine Withdrawal, Cocaine Intoxication Delirium, 5 Cocaine-Induced Psychotic Disorder with delusions, Cocaine-Induced Psychotic Disorders with hallucinations, Cocaine-Induced Mood Disorder, Cocaine-Induced Anxiety Disorder, Cocaine-Induced Sexual Dysfunction, Cocaine-Induced Sleep Disorder, Cocaine Related Disorder not otherwise specified (NOS), Cocaine Intoxication, and Cocaine Withdrawal.

Hallucinogen-related disorders include, but are not limited to, Hallucinogen 10 Dependence, Hallucinogen Abuse, Hallucinogen Intoxication, Hallucinogen Withdrawal, Hallucinogen Intoxication Delirium, Hallucinogen-Induced Psychotic Disorder with delusions, Hallucinogen-Induced Psychotic Disorders with hallucinations, Hallucinogen-Induced Mood Disorder, Hallucinogen-Induced Anxiety Disorder, Hallucinogen-Induced Sexual Dysfunction, Hallucinogen-Induced Sleep Disorder, 15 Hallucinogen Related Disorder not otherwise specified (NOS), Hallucinogen Intoxication, and Hallucinogen Persisting Perception Disorder (Flashbacks).

Inhalant-related disorders include, but are not limited to, Inhalant Dependence, Inhalant Abuse, Inhalant Intoxication, Inhalant Intoxication Delirium, Inhalant-Induced Psychotic Disorder with delusions, Inhalant-Induced Psychotic Disorder with hallucinations, 20 Inhalant-Induced Anxiety Disorder, Inhalant Related Disorder not otherwise specified (NOS), and Inhalant Intoxication.

Opioid-related disorders include, but are not limited to, Opioid Dependence, Opioid Abuse, Opioid Intoxication, Opioid Intoxication Delirium, Opioid-Induced Psychotic Disorder with delusions, Opioid-Induced Psychotic Disorder with hallucinations, 25 Opioid-Induced Anxiety Disorder, Opioid Related Disorder not otherwise specified (NOS), Opioid Intoxication, and Opioid Withdrawal.

The Cyanoiminopiperazine Compounds can be used to treat or prevent Parkinson's disease and parkinsonism and the symptoms associated with Parkinson's disease and parkinsonism, including but not limited to, bradykinesia, muscular rigidity, resting 30 tremor, and impairment of postural balance.

The Cyanoiminopiperazine Compounds can be used to treat or prevent generalized anxiety or severe anxiety and the symptoms associated with anxiety, including but not limited to, restlessness; tension; tachycardia; dyspnea; depression, including chronic “neurotic” depression; panic disorder; agoraphobia and other specific phobias; eating disorders; and personality disorders.

The Cyanoiminopiperazine Compounds can be used to treat or prevent epilepsy, including but not limited to, partial epilepsy, generalized epilepsy, and the symptoms associated with epilepsy, including but not limited to, simple partial seizures, jacksonian seizures, complex partial (psychomotor) seizures, convulsive seizures (grand mal or tonic-clonic seizures), petit mal (absence) seizures, and status epilepticus.

The Cyanoiminopiperazine Compounds can be used to treat or prevent strokes, including but not limited to, ischemic strokes and hemorrhagic strokes.

The Cyanoiminopiperazine Compounds can be used to treat or prevent a seizure, including but not limited to, infantile spasms, febrile seizures, and epileptic seizures.

The Cyanoiminopiperazine Compounds can be used to treat or prevent a pruritic condition, including but not limited to, pruritus caused by dry skin, scabies, dermatitis, herpetiformis, atopic dermatitis, *pruritus vulvae et ani*, miliaria, insect bites, pediculosis, contact dermatitis, drug reactions, urticaria, urticarial eruptions of pregnancy, psoriasis, lichen planus, lichen simplex chronicus, exfoliative dermatitis, folliculitis, bullous pemphigoid, or fiberglass dermatitis.

The Cyanoiminopiperazine Compounds can be used to treat or prevent psychosis, including but not limited to, schizophrenia, including paranoid schizophrenia, hebephrenic or disorganized schizophrenia, catatonic schizophrenia, undifferentiated schizophrenia, negative or deficit subtype schizophrenia, and non-deficit schizophrenia; a delusional disorder, including erotomanic subtype delusional disorder, grandiose subtype delusional disorder, jealous subtype delusional disorder, persecutory subtype delusional disorder, and somatic subtype delusional disorder; and brief psychosis.

The Cyanoiminopiperazine Compounds can be used to treat or prevent a cognitive disorder, including but not limited to, delirium and dementia such as multi-infarct dementia, dementia pugilistica, dementia caused by AIDS, and dementia caused by Alzheimer’s disease.

The Cyanoiminopiperazine Compounds can be used to treat or prevent a memory deficiency, including but not limited to, dissociative amnesia and dissociative fugue.

The Cyanoiminopiperazine Compounds can be used to treat or prevent restricted brain function, including but not limited to, that caused by surgery or an organ transplant, restricted blood supply to the brain, a spinal cord injury, a head injury, hypoxia, cardiac arrest, or hypoglycemia.

The Cyanoiminopiperazine Compounds can be used to treat or prevent Huntington's chorea.

The Cyanoiminopiperazine Compounds can be used to treat or prevent ALS.

The Cyanoiminopiperazine Compounds can be used to treat or prevent retinopathy, including but not limited to, arteriosclerotic retinopathy, diabetic arteriosclerotic retinopathy, hypertensive retinopathy, non-proliferative retinopathy, and proliferative retinopathy.

The Cyanoiminopiperazine Compounds can be used to treat or prevent a muscle spasm.

The Cyanoiminopiperazine Compounds can be used to treat or prevent a migraine.

The Cyanoiminopiperazine Compounds can be used to inhibit, treat or prevent vomiting, including but not limited to, nausea vomiting, dry vomiting (retching), and regurgitation.

The Cyanoiminopiperazine Compounds can be used to treat or prevent dyskinesia, including but not limited to, tardive dyskinesia and biliary dyskinesia.

The Cyanoiminopiperazine Compounds can be used to treat or prevent depression, including but not limited to, major depression and bipolar disorder.

Applicants believe that the Cyanoiminopiperazine Compounds are antagonists for VR1.

The invention also relates to methods for inhibiting VR1 function in a cell, comprising contacting a cell capable of expressing VR1 with an effective amount of a Cyanoiminopiperazine Compound. This method can be used *in vitro*, for example, as an assay to select cells that express VR1 and, accordingly, are useful as part of an assay to select compounds useful for treating or preventing pain, UI, an ulcer, IBD, or IBS. The method is

also useful for inhibiting VR1 function in a cell *in vivo*, in an animal, a human in one embodiment, by contacting a cell, in an animal, with an effective amount of a Cyanoiminopiperazine Compound. In one embodiment, the method is useful for treating or preventing pain in an animal. In another embodiment, the method is useful for treating or preventing UI in an animal. In another embodiment, the method is useful for treating or preventing an ulcer in an animal. In another embodiment, the method is useful for treating or preventing IBD in an animal. In another embodiment, the method is useful for treating or preventing IBS in an animal.

Examples of tissue comprising cells capable of expressing VR1 include, but are not limited to, neuronal, brain, kidney, urothelium, and bladder tissue. Methods for assaying cells that express VR1 are well known in the art.

Applicants believe that the Cyanoiminopiperazine Compounds are antagonists for mGluR5.

The invention also relates to methods for inhibiting mGluR5 function in a cell, comprising contacting a cell capable of expressing mGluR5 with an amount of a Cyanoiminopiperazine Compound effective to inhibit mGluR5 function in the cell. This method can be used *in vitro*, for example, as an assay to select cells that express mGluR5 and, accordingly, are useful as part of an assay to select compounds useful for treating or preventing pain, an addictive disorder, Parkinson's disease, parkinsonism, anxiety, a pruritic condition, or psychosis. The method is also useful for inhibiting mGluR5 function in a cell *in vivo*, in an animal, a human in one embodiment, by contacting a cell, in an animal, with an amount of a Cyanoiminopiperazine Compound effective to inhibit mGluR5 function in the cell. In one embodiment, the method is useful for treating or preventing pain in an animal in need thereof. In another embodiment, the method is useful for treating or preventing an addictive disorder in an animal in need thereof. In another embodiment, the method is useful for treating or preventing Parkinson's disease in an animal in need thereof. In another embodiment, the method is useful for treating or preventing parkinsonism in an animal in need thereof. In another embodiment, the method is useful for treating or preventing anxiety in an animal in need thereof. In another embodiment, the method is useful for treating or preventing a pruritic condition in an animal in need thereof. In another embodiment, the method is useful for treating or preventing psychosis in an animal in need thereof.

Examples of cells capable of expressing mGluR5 are neuronal and glial cells of the central nervous system, particularly the brain, especially in the nucleus accumbens. Methods for assaying cells that express mGluR5 are well known in the art.

Applicants believe that the Cyanoiminopiperazine Compounds are antagonists
5 for mGluR1.

The invention also relates to methods for inhibiting mGluR1 function in a cell, comprising contacting a cell capable of expressing mGluR1 with an amount of a Cyanoiminopiperazine Compound effective to inhibit mGluR1 function in the cell. This method can be used *in vitro*, for example, as an assay to select cells that express mGluR1 and,
10 accordingly, are useful as part of an assay to select compounds useful for treating or preventing pain, UI, an addictive disorder, Parkinson's disease, parkinsonism, anxiety, epilepsy, stroke, a seizure, a pruritic condition, psychosis, a cognitive disorder, a memory deficit, restricted brain function, Huntington's chorea, ALS, dementia, retinopathy, a muscle spasm, a migraine, vomiting, dyskinesia, or depression. The method is also useful for
15 inhibiting mGluR1 function in a cell *in vivo*, in an animal, a human in one embodiment, by contacting a cell, in an animal, with an amount of a Cyanoiminopiperazine Compound effective to inhibit mGluR1 function in the cell. In one embodiment, the method is useful for treating or preventing pain in an animal in need thereof. In another embodiment, the method is useful for treating or preventing UI in an animal in need thereof. In another embodiment,
20 the method is useful for treating or preventing an addictive disorder in an animal in need thereof. In another embodiment, the method is useful for treating or preventing Parkinson's disease in an animal in need thereof. In another embodiment, the method is useful for treating or preventing parkinsonism in an animal in need thereof. In another embodiment, the method is useful for treating or preventing anxiety in an animal in need thereof. In another
25 embodiment, the method is useful for treating or preventing epilepsy in an animal in need thereof. In another embodiment, the method is useful for treating or preventing stroke in an animal in need thereof. In another embodiment, the method is useful for treating or preventing a seizure in an animal in need thereof. In another embodiment, the method is useful for treating or preventing a pruritic condition in an animal in need thereof. In another
30 embodiment, the method is useful for treating or preventing psychosis in an animal in need thereof. In another embodiment, the method is useful for treating or preventing a cognitive

disorder in an animal in need thereof. In another embodiment, the method is useful for treating or preventing a memory deficit in an animal in need thereof. In another embodiment, the method is useful for treating or preventing restricted brain function in an animal in need thereof. In another embodiment, the method is useful for treating or preventing Huntington's chorea in an animal in need thereof. In another embodiment, the method is useful for treating or preventing ALS in an animal in need thereof. In another embodiment, the method is useful for treating or preventing dementia in an animal in need thereof. In another embodiment, the method is useful for treating or preventing retinopathy in an animal in need thereof. In another embodiment, the method is useful for treating or preventing a muscle spasm in an animal in need thereof. In another embodiment, the method is useful for treating or preventing a migraine in an animal in need thereof. In another embodiment, the method is useful for treating or preventing vomiting in an animal in need thereof. In another embodiment, the method is useful for treating or preventing dyskinesia in an animal in need thereof. In another embodiment, the method is useful for treating or preventing depression in an animal in need thereof.

Examples of cells capable of expressing mGluR1 include, but are not limited to, cerebellar Purkinje neuron cells, Purkinje cell bodies (punctate), cells of spine(s) of the cerebellum; neurons and neurophil cells of olfactory-bulb glomeruli; cells of the superficial layer of the cerebral cortex; hippocampus cells; thalamus cells; superior colliculus cells; and spinal trigeminal nucleus cells. Methods for assaying cells that express mGluR1 are well known in the art.

4.19.1 THERAPEUTIC/PROPHYLACTIC ADMINISTRATION AND COMPOSITIONS OF THE INVENTION

Due to their activity, the Cyanoiminopiperazine Compounds are advantageously useful in veterinary and human medicine. As described above, the Cyanoiminopiperazine Compounds are useful for treating or preventing pain, UI, an ulcer, IBD, IBS, an addictive disorder, Parkinson's disease, parkinsonism, anxiety, epilepsy, stroke, a seizure, a pruritic condition, psychosis, a cognitive disorder, a memory deficit, restricted brain function, Huntington's chorea, ALS, dementia, retinopathy, a muscle spasm, a migraine, vomiting, dyskinesia, or depression in an animal in need thereof.

When administered to an animal, the Cyanoiminopiperazine Compounds are administered as a component of a composition that comprises a pharmaceutically acceptable carrier or excipient. The present compositions, which comprise a Cyanoiminopiperazine Compound, can be administered orally. The Cyanoiminopiperazine Compounds of the
5 invention can also be administered by any other convenient route, for example, by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (*e.g.*, oral, rectal, and intestinal mucosa, *etc.*) and can be administered together with another biologically active agent. Administration can be systemic or local. Various delivery systems are known, *e.g.*, encapsulation in liposomes, microparticles, microcapsules, capsules, *etc.*, and can be used to
10 administer the Cyanoiminopiperazine Compound.

Methods of administration include, but are not limited to, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, oral, sublingual, intracerebral, intravaginal, transdermal, rectal, by inhalation, or topical, particularly to the ears, nose, eyes, or skin. The mode of administration is left to the
15 discretion of the practitioner. In most instances, administration will result in the release of the Cyanoiminopiperazine Compounds into the bloodstream.

In specific embodiments, it can be desirable to administer the Cyanoiminopiperazine Compounds locally. This can be achieved, for example, and not by way of limitation, by local infusion during surgery, topical application, *e.g.*, in conjunction
20 with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository or enema, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers.

In certain embodiments, it can be desirable to introduce the Cyanoiminopiperazine Compounds into the central nervous system or gastrointestinal tract by
25 any suitable route, including intraventricular, intrathecal, and epidural injection, and enema. Intraventricular injection can be facilitated by an intraventricular catheter, for example, attached to a reservoir, such as an Ommaya reservoir.

Pulmonary administration can also be employed, *e.g.*, by use of an inhaler or nebulizer, and formulation with an aerosolizing agent, or via perfusion in a fluorocarbon or
30 synthetic pulmonary surfactant. In certain embodiments, the Cyanoiminopiperazine

Compounds can be formulated as a suppository, with traditional binders and excipients such as triglycerides.

In another embodiment, the Cyanoiminopiperazine Compounds can be delivered in a vesicle, in particular a liposome (*see* Langer, *Science* 249:1527-1533 (1990) and Treat *et al.*, *Liposomes in the Therapy of Infectious Disease and Cancer* 317-327 and 353-365 (1989)).

In yet another embodiment, the Cyanoiminopiperazine Compounds can be delivered in a controlled-release system or sustained-release system (*see, e.g.*, Goodson, in *Medical Applications of Controlled Release*, *supra*, vol. 2, pp. 115-138 (1984)). Other controlled- or sustained-release systems discussed in the review by Langer, *Science* 249:1527-1533 (1990) can be used. In one embodiment, a pump can be used (Langer, *Science* 249:1527-1533 (1990); Sefton, *CRC Crit. Ref. Biomed. Eng.* 14:201 (1987); Buchwald *et al.*, *Surgery* 88:507 (1980); and Saudek *et al.*, *N. Engl. J. Med.* 321:574 (1989)). In another embodiment, polymeric materials can be used (*see Medical Applications of Controlled Release* (Langer and Wise eds., 1974); *Controlled Drug Bioavailability, Drug Product Design and Performance* (Smolen and Ball eds., 1984); Ranger and Peppas, *J. Macromol. Sci. Rev. Macromol. Chem.* 23:61 (1983); Levy *et al.*, *Science* 228:190 (1985); During *et al.*, *Ann. Neurol.* 25:351 (1989); and Howard *et al.*, *J. Neurosurg.* 71:105 (1989)). In yet another embodiment, a controlled- or sustained-release system can be placed in proximity of a target of the Cyanoiminopiperazine Compounds, *e.g.*, the spinal column, brain, or gastrointestinal tract, thus requiring only a fraction of the systemic dose.

The present compositions can optionally comprise a suitable amount of a pharmaceutically acceptable excipient so as to provide the form for proper administration to the animal.

Such pharmaceutical excipients can be liquids, such as water and oils, including those of petroleum, animal, vegetable, or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. The pharmaceutical excipients can be saline, gum acacia, gelatin, starch paste, talc, keratin, colloidal silica, urea and the like. In addition, auxiliary, stabilizing, thickening, lubricating, and coloring agents can be used. In one embodiment, the pharmaceutically acceptable excipients are sterile when administered to an animal. Water is a particularly useful excipient when the Cyanoiminopiperazine

Compound is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid excipients, particularly for injectable solutions. Suitable pharmaceutical excipients also include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The present compositions, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents.

The present compositions can take the form of solutions, suspensions, emulsion, tablets, pills, pellets, capsules, capsules containing liquids, powders, sustained-release formulations, suppositories, emulsions, aerosols, sprays, suspensions, or any other form suitable for use. In one embodiment, the composition is in the form of a capsule (see *e.g.*, U.S. Patent No. 5,698,155). Other examples of suitable pharmaceutical excipients are described in *Remington's Pharmaceutical Sciences* 1447-1676 (Alfonso R. Gennaro ed., 19th ed. 1995), incorporated herein by reference.

In one embodiment, the Cyanoiminopiperazine Compounds are formulated in accordance with routine procedures as a composition adapted for oral administration to human beings. Compositions for oral delivery can be in the form of tablets, lozenges, aqueous or oily suspensions, granules, powders, emulsions, capsules, syrups, or elixirs, for example. Orally administered compositions can contain one or more agents, for example, sweetening agents such as fructose, aspartame or saccharin; flavoring agents such as peppermint, oil of wintergreen, or cherry; coloring agents; and preserving agents, to provide a pharmaceutically palatable preparation. Moreover, where in tablet or pill form, the compositions can be coated to delay disintegration and absorption in the gastrointestinal tract thereby providing a sustained action over an extended period of time. Selectively permeable membranes surrounding an osmotically active driving compound are also suitable for orally administered compositions. In these latter platforms, fluid from the environment surrounding the capsule is imbibed by the driving compound, which swells to displace the agent or agent composition through an aperture. These delivery platforms can provide an essentially zero order delivery profile as opposed to the spiked profiles of immediate release formulations. A time-delay material such as glycerol monostearate or glycerol stearate can also be used. Oral compositions can include standard excipients such as mannitol, lactose, starch, magnesium

stearate, sodium saccharin, cellulose, and magnesium carbonate. In one embodiment, the excipients are of pharmaceutical grade.

In another embodiment, the Cyanoiminopiperazine Compounds can be formulated for intravenous administration. Typically, compositions for intravenous administration comprise sterile isotonic aqueous buffer. Where necessary, the compositions can also include a solubilizing agent. Compositions for intravenous administration can optionally include a local anesthetic such as lignocaine to lessen pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampule or sachette indicating the quantity of active agent. Where the Cyanoiminopiperazine Compounds are to be administered by infusion, they can be dispensed, for example, with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the Cyanoiminopiperazine Compounds are administered by injection, an ampule of sterile water for injection or saline can be provided so that the ingredients can be mixed prior to administration.

The Cyanoiminopiperazine Compounds can be administered by controlled-release or sustained-release means or by delivery devices that are well known to those of ordinary skill in the art. Examples include, but are not limited to, those described in U.S. Patent Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; 4,008,719; 5,674,533; 5,059,595; 5,591,767; 5,120,548; 5,073,543; 5,639,476; 5,354,556; and 5,733,566, each of which is incorporated herein by reference. Such dosage forms can be used to provide controlled- or sustained-release of one or more active ingredients using, for example, hydropropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, microspheres, or a combination thereof to provide the desired release profile in varying proportions. Suitable controlled- or sustained-release formulations known to those of ordinary skill in the art, including those described herein, can be readily selected for use with the active ingredients of the invention. The invention thus encompasses single unit dosage forms suitable for oral administration such as, but not limited to, tablets, capsules, gelcaps, and caplets that are adapted for controlled- or sustained-release.

Controlled- or sustained-release pharmaceutical compositions can have a common goal of improving drug therapy over that achieved by their non-controlled or non-

sustained counterparts. In one embodiment, a controlled- or sustained-release composition comprises a minimal amount of a Cyanoiminopiperazine Compound to cure or control the condition in a minimum amount of time. Advantages of controlled- or sustained-release compositions include extended activity of the drug, reduced dosage frequency, and increased patient compliance. In addition, controlled- or sustained-release compositions can favorably affect the time of onset of action or other characteristics, such as blood levels of the Cyanoiminopiperazine Compound, and can thus reduce the occurrence of adverse side effects.

Controlled- or sustained-release compositions can initially release an amount of a Cyanoiminopiperazine Compound that promptly produces the desired therapeutic or prophylactic effect, and gradually and continually release other amounts of the Cyanoiminopiperazine Compound to maintain this level of therapeutic or prophylactic effect over an extended period of time. To maintain a constant level of the Cyanoiminopiperazine Compound in the body, the Cyanoiminopiperazine Compound can be released from the dosage form at a rate that will replace the amount of Cyanoiminopiperazine Compound being metabolized and excreted from the body. Controlled- or sustained-release of an active ingredient can be stimulated by various conditions, including but not limited to, changes in pH, changes in temperature, concentration or availability of enzymes, concentration or availability of water, or other physiological conditions or compounds.

The amount of the Cyanoiminopiperazine Compound that is effective in the treatment or prevention of pain, UI, an ulcer, IBD, IBS, an addictive disorder, Parkinson's disease, parkinsonism, anxiety, epilepsy, stroke, a seizure, a pruritic condition, psychosis, a cognitive disorder, a memory deficit, restricted brain function, Huntington's chorea, ALS, dementia, retinopathy, a muscle spasm, a migraine, vomiting, dyskinesia, or depression and can be determined by standard clinical techniques. In addition, *in vitro* or *in vivo* assays can optionally be employed to help identify optimal dosage ranges. The precise dose to be employed will also depend on the route of administration, and the seriousness of the condition being treated and should be decided according to the judgment of the practitioner and each patient's circumstances in view of, *e.g.*, published clinical studies. Suitable effective dosage amounts, however, range from about 10 micrograms to about 2500 milligrams about every 4 h, although they are typically about 100 mg or less. In one embodiment, the effective

dosage amount ranges from about 0.01 milligrams to about 100 milligrams of a Cyanoiminopiperazine Compound about every 4 h, in another embodiment, about 0.020 milligrams to about 50 milligrams about every 4 h, and in another embodiment, about 0.025 milligrams to about 20 milligrams about every 4 h. The effective dosage amounts described
5 herein refer to total amounts administered; that is, if more than one Cyanoiminopiperazine Compound is administered, the effective dosage amounts correspond to the total amount administered.

Where a cell capable of expressing VR1, mGluR5, or mGluR1 is contacted with a Cyanoiminopiperazine Compound *in vitro*, the amount effective for inhibiting the
10 receptor function in a cell will typically range from about 0.01 $\mu\text{g/L}$ to about 5 mg/L, in one embodiment, from about 0.01 $\mu\text{g/L}$ to about 2.5 mg/L, in another embodiment, from about 0.01 $\mu\text{g/L}$ to about 0.5 mg/L, and in another embodiment, from about 0.01 $\mu\text{g/L}$ to about 0.25 mg/L of a solution or suspension of a pharmaceutically acceptable carrier or excipient. In one embodiment, the volume of solution or suspension is from about 1 μL to about 1 mL. In
15 another embodiment, the volume of solution or suspension is about 200 μL .

Where a cell capable of expressing VR1, mGluR5, or mGluR1 is contacted with a Cyanoiminopiperazine Compound *in vivo*, the amount effective for inhibiting the receptor function in a cell will typically range from about 0.01 mg to about 100 mg/kg of body weight per day, in one embodiment, from about 0.1 mg to about 50 mg/kg body weight
20 per day, and in another embodiment, from about 1 mg to about 20 mg/kg of body weight per day.

The Cyanoiminopiperazine Compounds can be assayed *in vitro* or *in vivo* for the desired therapeutic or prophylactic activity prior to use in humans. Animal model systems can be used to demonstrate safety and efficacy.

25 The present methods for treating or preventing pain, UI, an ulcer, IBD, IBS, an addictive disorder, Parkinson's disease, parkinsonism, anxiety, epilepsy, stroke, a seizure, a pruritic condition, psychosis, a cognitive disorder, a memory deficit, restricted brain function, Huntington's chorea, ALS, dementia, retinopathy, a muscle spasm, a migraine, vomiting, dyskinesia, or depression in an animal in need thereof can further comprise administering to
30 the animal being administered a Cyanoiminopiperazine Compound another therapeutic agent. In one embodiment, the other therapeutic agent is administered in an effective amount.

The present methods for inhibiting VR1 function in a cell capable of expressing VR1 can further comprise contacting the cell with an effective amount of another therapeutic agent.

5 The present methods for inhibiting mGluR5 function in a cell capable of expressing mGluR5 can further comprise contacting the cell with an effective amount of another therapeutic agent.

The present methods for inhibiting mGluR1 function in a cell capable of expressing mGluR1 can further comprise contacting the cell with an effective amount of another therapeutic agent.

10 The other therapeutic agent includes, but is not limited to, an opioid agonist, a non-opioid analgesic, a non-steroid anti-inflammatory agent, an antimigraine agent, a Cox-II inhibitor, an antiemetic, a β -adrenergic blocker, an anticonvulsant, an antidepressant, a Ca²⁺-channel blocker, an anticancer agent, an agent for treating or preventing UI, an agent for treating or preventing an ulcer, an agent for treating or preventing IBD, an agent for
15 treating or preventing IBS, an agent for treating addictive disorder, an agent for treating Parkinson's disease and parkinsonism, an agent for treating anxiety, an agent for treating epilepsy, an agent for treating a stroke, an agent for treating a seizure, an agent for treating a pruritic condition, an agent for treating psychosis, an agent for treating Huntington's chorea, an agent for treating ALS, an agent for treating a cognitive disorder, an agent for treating a
20 migraine, an agent for treating vomiting, an agent for treating dyskinesia, or an agent for treating depression, and mixtures thereof.

Effective amounts of the other therapeutic agents are well known to those skilled in the art. However, it is well within the skilled artisan's purview to determine the other therapeutic agent's optimal effective-amount range. In one embodiment of the
25 invention, where another therapeutic agent is administered to an animal, the effective amount of the Cyanoiminopiperazine Compound is less than its effective amount would be where the other therapeutic agent is not administered. In this case, without being bound by theory, it is believed that the Cyanoiminopiperazine Compounds and the other therapeutic agent act synergistically to treat or prevent pain, UI, an ulcer, IBD, IBS, an addictive disorder,
30 Parkinson's disease, parkinsonism, anxiety, epilepsy, stroke, a seizure, a pruritic condition, psychosis, a cognitive disorder, a memory deficit, restricted brain function, Huntington's

chorea, ALS, dementia, retinopathy, a muscle spasm, a migraine, vomiting, dyskinesia, or depression.

Examples of useful opioid agonists include, but are not limited to, alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, 5 butorphanol, clonitazene, codeine, desomorphine, dextromoramide, dezocine, diampromide, diamorphine, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene fentanyl, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levorphanol, 10 levophenacylmorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, nalbuphine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, proheptazine, promedol, properidine, propiram, propoxyphene, sufentanil, 15 tilidine, tramadol, pharmaceutically acceptable salts thereof, and mixtures thereof.

In certain embodiments, the opioid agonist is selected from codeine, hydromorphone, hydrocodone, oxycodone, dihydrocodeine, dihydromorphine, morphine, tramadol, oxymorphone, pharmaceutically acceptable salts thereof, and mixtures thereof.

20 Examples of useful non-opioid analgesics include non-steroidal anti-inflammatory agents, such as aspirin, ibuprofen, diclofenac, naproxen, benoxaprofen, flurbiprofen, fenoprofen, flubufen, ketoprofen, indoprofen, piroprofen, carprofen, oxaprozin, pramoprofen, muprofen, trioxaprofen, suprofen, aminoprofen, tiaprofenic acid, fluprofen, bucloxic acid, indomethacin, sulindac, tolmetin, zomepirac, tiopinac, zidometacin, 25 acemetacin, fentiazac, clidanac, oxpinac, mefenamic acid, meclofenamic acid, flufenamic acid, niflumic acid, tolfenamic acid, diflurisal, flufenisal, piroxicam, sudoxicam, isoxicam, and pharmaceutically acceptable salts thereof, and mixtures thereof. Other suitable non-opioid analgesics include the following, non-limiting, chemical classes of analgesic, antipyretic, nonsteroidal anti-inflammatory drugs: salicylic acid derivatives, including 30 aspirin, sodium salicylate, choline magnesium trisalicylate, salsalate, diflunisal, salicylsalicylic acid, sulfasalazine, and olsalazin; para-aminophenol derivatives including

acetaminophen and phenacetin; indole and indene acetic acids, including indomethacin, sulindac, and etodolac; heteroaryl acetic acids, including tolmetin, diclofenac, and ketorolac; anthranilic acids (fenamates), including mefenamic acid and meclofenamic acid; enolic acids, including oxicams (piroxicam, tenoxicam), and pyrazolidinediones (phenylbutazone, oxyphenthartazone); and alkanones, including nabumetone. For a more detailed description of the NSAIDs, see *Paul A. Insel, Analgesic-Antipyretic and Anti-inflammatory Agents and Drugs Employed in the Treatment of Gout, in Goodman & Gilman's The Pharmacological Basis of Therapeutics* 617-57 (Perry B. Molinoff and Raymond W. Ruddon eds., 9th ed 1996) and Glen R. Hanson, *Analgesic, Antipyretic and Anti-Inflammatory Drugs in Remington: The Science and Practice of Pharmacy Vol II* 1196-1221 (A.R. Gennaro ed. 19th ed. 1995) which are hereby incorporated by reference in their entireties.

Examples of useful Cox-II inhibitors and 5-lipoxygenase inhibitors, as well as combinations thereof, are described in U.S. Patent No. 6,136,839, which is hereby incorporated by reference in its entirety. Examples of useful Cox-II inhibitors include, but are not limited to, rofecoxib and celecoxib.

Examples of useful antimigraine agents include, but are not limited to, alpiropride, dihydroergotamine, dolasetron, ergocornine, ergocorninine, ergocryptine, ergot, ergotamine, flumetrolone acetate, fonazine, lisuride, lomerizine, methysergide oxetorone, pizotyline, and mixtures thereof.

The other therapeutic agent can also be an agent useful for reducing any potential side effects of a Cyanoiminopiperazine Compounds. For example, the other therapeutic agent can be an antiemetic agent. Examples of useful antiemetic agents include, but are not limited to, metoclopramide, domperidone, prochlorperazine, promethazine, chlorpromazine, trimethobenzamide, ondansetron, granisetron, hydroxyzine, acetylleucine monoethanolamine, alizapride, azasetron, benzquinamide, biantanautine, bromopride, buclizine, clebopride, cyclizine, dimenhydrinate, diphenidol, dolasetron, meclizine, methallatal, metopimazine, nabilone, oxypendyl, pipamazine, scopolamine, sulpiride, tetrahydrocannabinol, thiethylperazine, thioproperazine, tropisetron, and mixtures thereof.

Examples of useful β -adrenergic blockers include, but are not limited to, acebutolol, alprenolol, amosulabol, arotinolol, atenolol, befunolol, betaxolol, bevantolol, bisoprolol, bopindolol, bucumolol, bufetolol, bufuralol, bunitrolol, bupranolol, butidrine

hydrochloride, butofilolol, carazolol, carteolol, carvedilol, celiprolol, cetamolol, cloranolol, dilevalol, epanolol, esmolol, indenolol, labetalol, levobunolol, mepindolol, metipranolol, metoprolol, moprolol, nadolol, nadoxolol, nebivalol, nifenalol, nipradilol, oxprenolol, penbutolol, pindolol, practolol, pronethalol, propranolol, sotalol, sulfinalol, talinolol, 5 tertatolol, tilisolol, timolol, toliprolol, and xibenolol.

Examples of useful anticonvulsants include, but are not limited to, acetylpheneturide, albutoin, aloxidone, aminoglutethimide, 4-amino-3-hydroxybutyric acid, atrolactamide, beclamide, buramate, calcium bromide, carbamazepine, cinromide, clomethiazole, clonazepam, decimemide, diethadione, dimethadione, doxenitroin, eterobarb, 10 ethadione, ethosuximide, ethotoin, felbamate, fluoresone, gabapentin, 5-hydroxytryptophan, lamotrigine, magnesium bromide, magnesium sulfate, mephenytoin, mephobarbital, metharbital, methetoin, methsuximide, 5-methyl-5-(3-phenanthryl)-hydantoin, 3-methyl-5-phenylhydantoin, narcobarbital, nimetazepam, nitrazepam, oxcarbazepine, paramethadione, phenacemide, phenetharbital, pheneturide, phenobarbital, phensuximide, 15 phenylmethylbarbituric acid, phenytoin, phethenylate sodium, potassium bromide, pregabalin, primidone, progabide, sodium bromide, solanum, strontium bromide, suclofenide, sulthiame, tetrantoin, tiagabine, topiramate, trimethadione, valproic acid, valpromide, vigabatrin, and zonisamide.

Examples of useful antidepressants include, but are not limited to, binedaline, 20 caroxazone, citalopram, dimethazan, fencamine, indalpine, indeloxazine hydrochloride, nefopam, nomifensine, oxitriptan, oxypertine, paroxetine, sertraline, thiazesim, trazodone, benmoxine, iproclozide, iproniazid, isocarboxazid, nialamide, octamoxin, phenelzine, cotinine, rolicyprine, rolipram, maprotiline, metralindole, mianserin, mirtazepine, adinazolam, amitriptyline, amitriptylinoxide, amoxapine, butriptyline, clomipramine, 25 demexiptiline, desipramine, dibenzepin, dimetacrine, dothiepin, doxepin, fluacizine, imipramine, imipramine N-oxide, iprindole, lofepramine, melitracen, metapramine, nortriptyline, noxiptilin, opipramol, pizotyline, propizepine, protriptyline, quinupramine, tianeptine, trimipramine, adrafinil, benactyzine, bupropion, butacetin, dioxadrol, duloxetine, etoperidone, febarbamate, femoxetine, fenpentadiol, fluoxetine, fluvoxamine, 30 hematoporphyrin, hypericin, levophacetoperane, medifoxamine, milnacipran, minaprine, moclobemide, nefazodone, oxaflorazone, piberaline, prolintane, pyrisuccideanol, ritanserin,

roxindole, rubidium chloride, sulpiride, tandospirone, thozalinone, tofenacin, toloxatone, tranlycypromine, L-tryptophan, venlafaxine, viloxazine, and zimeldine.

Examples of useful Ca²⁺-channel blockers include, but are not limited to, bepridil, clentiazem, diltiazem, fendiline, gallopamil, mibefradil, prenylamine, semotiadil, 5 terodiline, verapamil, amlodipine, aranidipine, barnidipine, benidipine, cilnidipine, efonidipine, elgodipine, felodipine, isradipine, lacidipine, lercanidipine, manidipine, nicardipine, nifedipine, nilvadipine, nimodipine, nisoldipine, nitrendipine, cinnarizine, flunarizine, lidoflazine, lomerizine, bencyclane, etafenone, fantofarone, and perhexiline.

Examples of useful anticancer agents include, but are not limited to, acivicin, 10 aclarubicin, acodazole hydrochloride, acronine, adozelesin, aldesleukin, altretamine, ambomycin, ametantrone acetate, aminoglutethimide, amsacrine, anastrozole, anthramycin, asparaginase, asperlin, azacitidine, azetepa, azotomycin, batimastat, benzodepa, bicalutamide, bisantrene hydrochloride, bisnafide dimesylate, bizelesin, bleomycin sulfate, brequinar sodium, bropirimine, busulfan, cactinomycin, calusterone, caracemide, carbetimer, 15 carboplatin, carmustine, carubicin hydrochloride, carzelesin, cedefingol, chlorambucil, cirolemycin, cisplatin, cladribine, crisnatol mesylate, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, daunorubicin hydrochloride, decitabine, dexormaplatin, dezaguanine, dezaguanine mesylate, diaziquone, docetaxel, doxorubicin, doxorubicin hydrochloride, droloxifene, droloxifene citrate, dromostanolone propionate, duazomycin, 20 edatrexate, eflornithine hydrochloride, elsamitrucin, enloplatin, enpromate, epipropidine, epirubicin hydrochloride, erbulozole, esorubicin hydrochloride, estramustine, estramustine phosphate sodium, etanidazole, etoposide, etoposide phosphate, etoprine, fadrozole hydrochloride, fazarabine, fenretinide, floxuridine, fludarabine phosphate, fluorouracil, flurocitabine, fosquidone, fostriecin sodium, gemcitabine, gemcitabine hydrochloride, 25 hydroxyurea, idarubicin hydrochloride, ifosfamide, ilmofofosine, interleukin II (including recombinant interleukin II or rIL2), interferon alfa-2a, interferon alfa-2b, interferon alfa-n1 , interferon alfa-n3, interferon beta-I a, interferon gamma-I b, iproplatin, irinotecan hydrochloride, lanreotide acetate, letrozole, leuprolide acetate, liarozole hydrochloride, lometrexol sodium, lomustine, losoxantrone hydrochloride, masoprocol, maytansine, 30 mechlorethamine hydrochloride, megestrol acetate, melengestrol acetate, melphalan, menogaril, mercaptopurine, methotrexate, methotrexate sodium, metoprine, meturedopa,

mitindomide, mitocarcin, mitocromin, mitogillin, mitomalcin, mitomycin, mitosper,
mitotane, mitoxantrone hydrochloride, mycophenolic acid, nocodazole, nogalamycin,
ormaplatin, oxisuran, paclitaxel, pegaspargase, peliomycin, pentamustine, peplomycin
sulfate, perfosfamide, pipobroman, piposulfan, piroxantrone hydrochloride, plicamycin,
5 plomestane, porfimer sodium, porfiromycin, prednimustine, procarbazine hydrochloride,
puromycin, puromycin hydrochloride, pyrazofurin, riboprime, rogletimide, safangol, safangol
hydrochloride, semustine, simtrazene, sparfosate sodium, sparsomycin, spirogermanium
hydrochloride, spiromustine, spiroplatin, streptonigrin, streptozocin, sulofenur, talisomycin,
tecogalan sodium, tegafur, teloxantrone hydrochloride, temoporfin, teniposide, teroxirone,
10 testolactone, thiamiprine, thioguanine, thiotepa, tiazofurin, tirapazamine, toremifene citrate,
trestolone acetate, tricyribine phosphate, trimetrexate, trimetrexate glucuronate, triptorelin,
tubulazole hydrochloride, uracil mustard, uredepa, vapreotide, verteporfin, vinblastine
sulfate, vincristine sulfate, vindesine, vindesine sulfate, vinepidine sulfate, vinglycinat
sulfate, vinleurosine sulfate, vinorelbine tartrate, vinrosidine sulfate, vinzolidine sulfate,
15 vorozole, zeniplatin, zinostatin, zorubicin hydrochloride.

Examples of other anti-cancer drugs include, but are not limited to,
20-epi-1,25 dihydroxyvitamin D3; 5-ethynyluracil; abiraterone; aclarubicin; acylfulvene;
adecypenol; adozelesin; aldesleukin; ALL-TK antagonists; altretamine; ambamustine;
amidox; amifostine; aminolevulinic acid; amrubicin; amsacrine; anagrelide; anastrozole;
20 andrographolide; angiogenesis inhibitors; antagonist D; antagonist G; antarelix;
anti-dorsalizing morphogenetic protein-1; antiandrogen, prostatic carcinoma; antiestrogen;
antineoplaston; antisense oligonucleotides; aphidicolin glycinate; apoptosis gene modulators;
apoptosis regulators; apurinic acid; ara-CDP-DL-PTBA; arginine deaminase; asulacrine;
atamestane; atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azasetron; azatoxin;
25 azatyrosine; baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists;
benzochlorins; benzoylstauroporine; beta lactam derivatives; beta-alethine; betaclamycin B;
betulinic acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine; bisnafide;
bistratene A; bizelesin; breflate; bropirimine; budotitane; buthionine sulfoximine;
calcipotriol; calphostin C; camptothecin derivatives; canarypox IL-2; capecitabine;
30 carboxamide-amino-triazole; carboxyamidotriazole; CaRest M3; CARN 700; cartilage
derived inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cecropin B;

cetorelix; chlorins; chloroquinoxaline sulfonamide; cicaprost; cis-porphyrin; cladribine;
 clomifene analogues; clotrimazole; collismycin A; collismycin B; combretastatin A4;
 combretastatin analogue; conagenin; crambescidin 816; crisnatol; cryptophycin 8;
 cryptophycin A derivatives; curacin A; cyclopentantraquinones; cycloplatam; cypemycin;
 5 cytarabine ocfosfate; cytolytic factor; cytostatin; dacliximab; decitabine; dehydrodidemnin B;
 deslorelin; dexamethasone; dexifosfamide; dexrazoxane; dexverapamil; diaziquone;
 didemnin B; didox; diethylnorspermine; dihydro-5-azacytidine; dihydrotaxol, 9-; dioxamycin;
 diphenyl spiromustine; docetaxel; docosanol; dolasetron; doxifluridine; droloxifene;
 dronabinol; duocarmycin SA; ebselen; ecomustine; edelfosine; edrecolomab; eflornithine;
 10 elemene; emitefur; epirubicin; epristeride; estramustine analogue; estrogen agonists; estrogen
 antagonists; etanidazole; etoposide phosphate; exemestane; fadrozole; fazarabine; fenretinide;
 filgrastim; finasteride; flavopiridol; flezelastine; fluasterone; fludarabine; fluorodaunorubicin
 hydrochloride; forfenimex; formestane; fostriecin; fotemustine; gadolinium texaphyrin;
 gallium nitrate; galocitabine; ganirelix; gelatinase inhibitors; gemcitabine; glutathione
 15 inhibitors; hepsulfam; heregulin; hexamethylene bisacetamide; hypericin; ibandronic acid;
 idarubicin; idoxifene; idramantone; ilmofosine; ilomastat; imidazoacridones; imiquimod;
 immunostimulant peptides; insulin-like growth factor-1 receptor inhibitor; interferon
 agonists; interferons; interleukins; iobenguane; iododoxorubicin; ipomeanol, 4-; iroplact;
 irsogladine; isobengazole; isohomohalicondrin B; itasetron; jasplakinolide; kahalalide F;
 20 lamellarin-N triacetate; lanreotide; leinamycin; lenograstim; lentinan sulfate; leptolstatin;
 letrozole; leukemia inhibiting factor; leukocyte alpha interferon;
 leuprolide+estrogen+progesterone; leuprorelin; levamisole; liarozole; linear polyamine
 analogue; lipophilic disaccharide peptide; lipophilic platinum compounds; lissoclinamide 7;
 lobaplatin; lombricine; lometrexol; lonidamine; losoxantrone; lovastatin; loxoribine;
 25 lurtotecan; lutetium texaphyrin; lysofylline; lytic peptides; maitansine; mannostatin A;
 marimastat; masoprocot; maspin; matrilysin inhibitors; matrix metalloproteinase inhibitors;
 menogaril; merbarone; meterelin; methioninase; metoclopramide; MIF inhibitor;
 mifepristone; miltefosine; mirimostim; mismatched double stranded RNA; mitoguazone;
 mitolactol; mitomycin analogues; mitonafide; mitotoxin fibroblast growth factor-saporin;
 30 mitoxantrone; mofarotene; molgramostim; monoclonal antibody, human chorionic
 gonadotrophin; monophosphoryl lipid A+myobacterium cell wall sk; mopidamol; multiple

drug resistance gene inhibitor; multiple tumor suppressor 1-based therapy; mustard anticancer agent; mycaperoxide B; mycobacterial cell wall extract; myriaporone; N-acetyldinaline; N-substituted benzamides; nafarelin; nagrestip; naloxone+pentazocine; napavin; naphterpin; nartograstim; nedaplatin; nemorubicin; neridronic acid; neutral endopeptidase; nilutamide;

5 nisamycin; nitric oxide modulators; nitroxide antioxidant; nitrullyn; O6-benzylguanine; octreotide; okicenone; oligonucleotides; onapristone; ondansetron; ondansetron; oracin; oral cytokine inducer; ormaplatin; osaterone; oxaliplatin; oxaunomycin; paclitaxel; paclitaxel analogues; paclitaxel derivatives; palauamine; palmitoylrhizoxin; pamidronic acid; panaxytriol; panomifene; parabactin; pazelliptine; pegaspargase; peldesine; pentosan

10 polysulfate sodium; pentostatin; pentrozole; perflubron; perfosfamide; perillyl alcohol; phenazinomycin; phenylacetate; phosphatase inhibitors; picibanil; pilocarpine hydrochloride; pirarubicin; piritrexim; placetin A; placetin B; plasminogen activator inhibitor; platinum complex; platinum compounds; platinum-triamine complex; porfimer sodium; porfiromycin; prednisone; propyl bis-acridone; prostaglandin J2; proteasome inhibitors; protein A-based

15 immune modulator; protein kinase C inhibitor; protein kinase C inhibitors, microalgal; protein tyrosine phosphatase inhibitors; purine nucleoside phosphorylase inhibitors; purpurins; pyrazoloacridine; pyridoxylated hemoglobin polyoxyethylene conjugate; raf antagonists; raltitrexed; ramosetron; ras farnesyl protein transferase inhibitors; ras inhibitors; ras-GAP inhibitor; retelliptine demethylated; rhenium Re 186 etidronate; rhizoxin;

20 ribozymes; RII retinamide; rogletimide; rohitukine; romurtide; roquinimex; rubiginone B1; ruboxyl; safingol; saintopin; SarCNU; sarcophytol A; sargramostim; Sdi 1 mimetics; semustine; senescence derived inhibitor 1; sense oligonucleotides; signal transduction inhibitors; signal transduction modulators; single chain antigen binding protein; sizofiran; sobuzoxane; sodium borocaptate; sodium phenylacetate; solverol; somatomedin binding

25 protein; sonermin; sparfosic acid; spicamycin D; spiromustine; splenopentin; spongistatin 1; squalamine; stem cell inhibitor; stem-cell division inhibitors; stipiamide; stromelysin inhibitors; sulfinosine; superactive vasoactive intestinal peptide antagonist; suradista; suramin; swainsonine; synthetic glycosaminoglycans; tallimustine; tamoxifen methiodide; tauromustine; tazarotene; tecogalan sodium; tegafur; tellurapyrylium; telomerase inhibitors;

30 temoporfin; temozolomide; teniposide; tetrachlorodecaoxide; tetrazomine; thaliblastine; thiocoraline; thrombopoietin; thrombopoietin mimetic; thymalfasin; thymopoietin receptor

agonist; thymotrigan; thyroid stimulating hormone; tin ethyl etiopurpurin; tirapazamine; titanocene bichloride; toposentin; toremifene; totipotent stem cell factor; translation inhibitors; tretinoin; triacetyluridine; tricycluridine; trimetrexate; triptorelin; tropisetron; turosteride; tyrosine kinase inhibitors; tyrophostins; UBC inhibitors; ubenimex; urogenital sinus-derived growth inhibitory factor; urokinase receptor antagonists; vapreotide; variolin B; vector system, erythrocyte gene therapy; velaresol; veramine; verdins; verteporfin; vinorelbine; vinorelbine; vitaxin; vorozole; zanoterone; zeniplatin; zilascorb; and zinostatin stimalamer.

Examples of useful therapeutic agents for treating or preventing UI include, but are not limited to, propantheline, imipramine, hyoscyamine, oxybutynin, and dicyclomine.

10 Examples of useful therapeutic agents for treating or preventing an ulcer include, antacids such as aluminum hydroxide, magnesium hydroxide, sodium bicarbonate, and calcium bicarbonate; sucralfate; bismuth compounds such as bismuth subsalicylate and bismuth subcitrate; H₂ antagonists such as cimetidine, ranitidine, famotidine, and nizatidine; H⁺, K⁺ - ATPase inhibitors such as omeprazole, lansoprazole, and lansoprazole; 15 carbenoxolone; misoprostol; and antibiotics such as tetracycline, metronidazole, tinidazole, clarithromycin, and amoxicillin.

 Examples of useful therapeutic agents for treating or preventing IBD include, but are not limited to, anticholinergic drugs; diphenoxylate; loperamide; deodorized opium tincture; codeine; broad-spectrum antibiotics such as metronidazole; sulfasalazine; olsalazine; 20 mesalamine; prednisone; azathioprine; mercaptopurine; and methotrexate.

 Examples of useful therapeutic agents for treating or preventing IBS include, but are not limited to, propantheline; muscarine receptor antagonists such as pirenzapine, methoctramine, ipratropium, tiotropium, scopolamine, methscopolamine, homatropine, homatropine methylbromide, and methantheline; and antidiarrheal drugs such as 25 diphenoxylate and loperamide.

 Examples of useful therapeutic agents for treating or preventing an addictive disorder include, but are not limited to, methadone, desipramine, amantadine, fluoxetine, buprenorphine, an opiate agonist, 3-phenoxypyridine, levomethadyl acetate hydrochloride, and serotonin antagonists.

30 Examples of useful therapeutic agents for treating or preventing Parkinson's disease and parkinsonism include, but are not limited to, carbidopa/levodopa, pergolide,

bromocriptine, ropinirole, pramipexole, entacapone, tolcapone, selegiline, amantadine, and trihexyphenidyl hydrochloride.

Examples of useful therapeutic agents for treating or preventing anxiety include, but are not limited to, benzodiazepines, such as alprazolam, brotizolam, 5 chlordiazepoxide, clobazam, clonazepam, clorazepate, demoxepam, diazepam, estazolam, flumazenil, flurazepam, halazepam, lorazepam, midazolam, nitrazepam, nordazepam, oxazepam, prazepam, quazepam, temazepam, and triazolam; non-benzodiazepine agents, such as buspirone, gepirone, ipsapirone, tiospirone, zolpicone, zolpidem, and zaleplon; tranquilizers, such as barbituates, *e.g.*, amobarbital, aprobarbital, butabarbital, butalbital, 10 mephobarbital, methohexital, pentobarbital, phenobarbital, secobarbital, and thiopental; and propanediol carbamates, such as meproamate and tybamate.

Examples of useful therapeutic agents for treating or preventing epilepsy include, but are not limited to, carbamazepine, ethosuximide, gabapentin, lamotrigine, phenobarbital, phenytoin, primidone, valproic acid, trimethadione, benzodiazepines, 15 gabapentin, lamotrigine, γ -vinyl GABA, acetazolamide, and felbamate.

Examples of useful therapeutic agents for treating or preventing stroke include, but are not limited to, anticoagulants such as heparin, agents that break up clots such as streptokinase or tissue plasminogen activator, agents that reduce swelling such as mannitol or corticosteroids, and acetylsalicylic acid.

20 Examples of useful therapeutic agents for treating or preventing a seizure include, but are not limited to, carbamazepine, ethosuximide, gabapentin, lamotrigine, phenobarbital, phenytoin, primidone, valproic acid, trimethadione, benzodiazepines, gabapentin, lamotrigine, γ -vinyl GABA, acetazolamide, and felbamate.

Examples of useful therapeutic agents for treating or preventing a pruritic 25 condition include, but are not limited to, naltrexone; nalmefene; danazol; tricyclics such as amitriptyline, imipramine, and doxepin; antidepressants such as those given below, menthol; camphor; phenol; pramoxine; capsaicin; tar; steroids; and antihistamines.

Examples of useful therapeutic agents for treating or preventing psychosis include, but are not limited to, phenothiazines such as chlorpromazine hydrochloride, 30 mesoridazine besylate, and thioridazine hydrochloride; thioxanthenes such as chlorprothixene and thiothixene hydrochloride; clozapine; risperidone; olanzapine;

quetiapine; quetiapine fumarate; haloperidol; haloperidol decanoate; loxapine succinate; molindone hydrochloride; pimozide; and ziprasidone.

Examples of useful therapeutic agents for treating or preventing Huntington's chorea include, but are not limited to, haloperidol and pimozide.

5 Examples of useful therapeutic agents for treating or preventing ALS include, but are not limited to, baclofen, neurotrophic factors, riluzole, tizanidine, benzodiazepines such as clonazepam and dantrolene.

 Examples of useful therapeutic agents for treating or preventing cognitive disorders include, but are not limited to, agents for treating or preventing dementia such as
10 tacrine; donepezil; ibuprofen; antipsychotic drugs such as thioridazine and haloperidol; and antidepressant drugs such as those given below.

 Examples of useful therapeutic agents for treating or preventing a migraine include, but are not limited to, sumatriptan; methysergide; ergotamine; caffeine; and beta-blockers such as propranolol, verapamil, and divalproex.

15 Examples of useful therapeutic agents for treating or preventing vomiting include, but are not limited to, 5-HT₃ receptor antagonists such as ondansetron, dolasetron, granisetron, and tropisetron; dopamine receptor antagonists such as prochlorperazine, thiethylperazine, chlorpromazine, metoclopramide, and domperidone; glucocorticoids such as dexamethasone; and benzodiazepines such as lorazepam and alprazolam.

20 Examples of useful therapeutic agents for treating or preventing dyskinesia include, but are not limited to, reserpine and tetrabenazine.

 Examples of useful therapeutic agents for treating or preventing depression include, but are not limited to, tricyclic antidepressants such as amitriptyline, amoxapine, bupropion, clomipramine, desipramine, doxepin, imipramine, maprotiline, nefazadone,
25 nortriptyline, protriptyline, trazodone, trimipramine, and venlafaxine; selective serotonin reuptake inhibitors such as fluoxetine, fluvoxamine, paroxetine, and setraline; monoamine oxidase inhibitors such as isocarboxazid, pargyline, phenelzine, and tranylcypromine; and psychostimulants such as dextroamphetamine and methylphenidate.

 A Cyanoiminopiperazine Compound and the other therapeutic agent can act
30 additively or, in one embodiment, synergistically. In one embodiment, a Cyanoiminopiperazine Compound is administered concurrently with another therapeutic

agent. In one embodiment, a composition comprising an effective amount of a Cyanoiminopiperazine Compound and an effective amount of another therapeutic agent can be administered. Alternatively, a composition comprising an effective amount of a Cyanoiminopiperazine Compound and a different composition comprising an effective amount of another therapeutic agent can be concurrently administered. In another embodiment, an effective amount of a Cyanoiminopiperazine Compound is administered prior or subsequent to administration of an effective amount of another therapeutic agent. In this embodiment, the Cyanoiminopiperazine Compound is administered while the other therapeutic agent exerts its therapeutic effect, or the other therapeutic agent is administered while the Cyanoiminopiperazine Compound exerts its preventative or therapeutic effect for treating or preventing a Condition.

A composition of the invention is prepared by a method comprising admixing a Cyanoiminopiperazine Compound or a pharmaceutically acceptable salt and a pharmaceutically acceptable carrier or excipient. Admixing can be accomplished using methods well known for admixing a compound (or salt) and a pharmaceutically acceptable carrier or excipient. In one embodiment the Cyanoiminopiperazine Compound or the pharmaceutically acceptable salt of the Compound is present in the composition in an effective amount.

20 **4.19.2 Kits**

The invention encompasses kits that can simplify the administration of a Cyanoiminopiperazine Compound to an animal.

A typical kit of the invention comprises a unit dosage form of a Cyanoiminopiperazine Compound. In one embodiment, the unit dosage form is a container, which can be sterile, containing an effective amount of a Cyanoiminopiperazine Compound and a pharmaceutically acceptable carrier or excipient. The kit can further comprise a label or printed instructions instructing the use of the Cyanoiminopiperazine Compound to treat pain, UI, an ulcer, IBD, IBS, an addictive disorder, Parkinson's disease, parkinsonism, anxiety, epilepsy, stroke, a seizure, a pruritic condition, psychosis, a cognitive disorder, a memory deficit, restricted brain function, Huntington's chorea, ALS, dementia, retinopathy, a muscle spasm, a migraine, vomiting, dyskinesia, or depression. The kit can also further comprise a

unit dosage form of another therapeutic agent, for example, a container containing an effective amount of the other therapeutic agent. In one embodiment, the kit comprises a container containing an effective amount of a Cyanoiminopiperazine Compound and an effective amount of another therapeutic agent. Examples of other therapeutic agents include,
5 but are not limited to, those listed above.

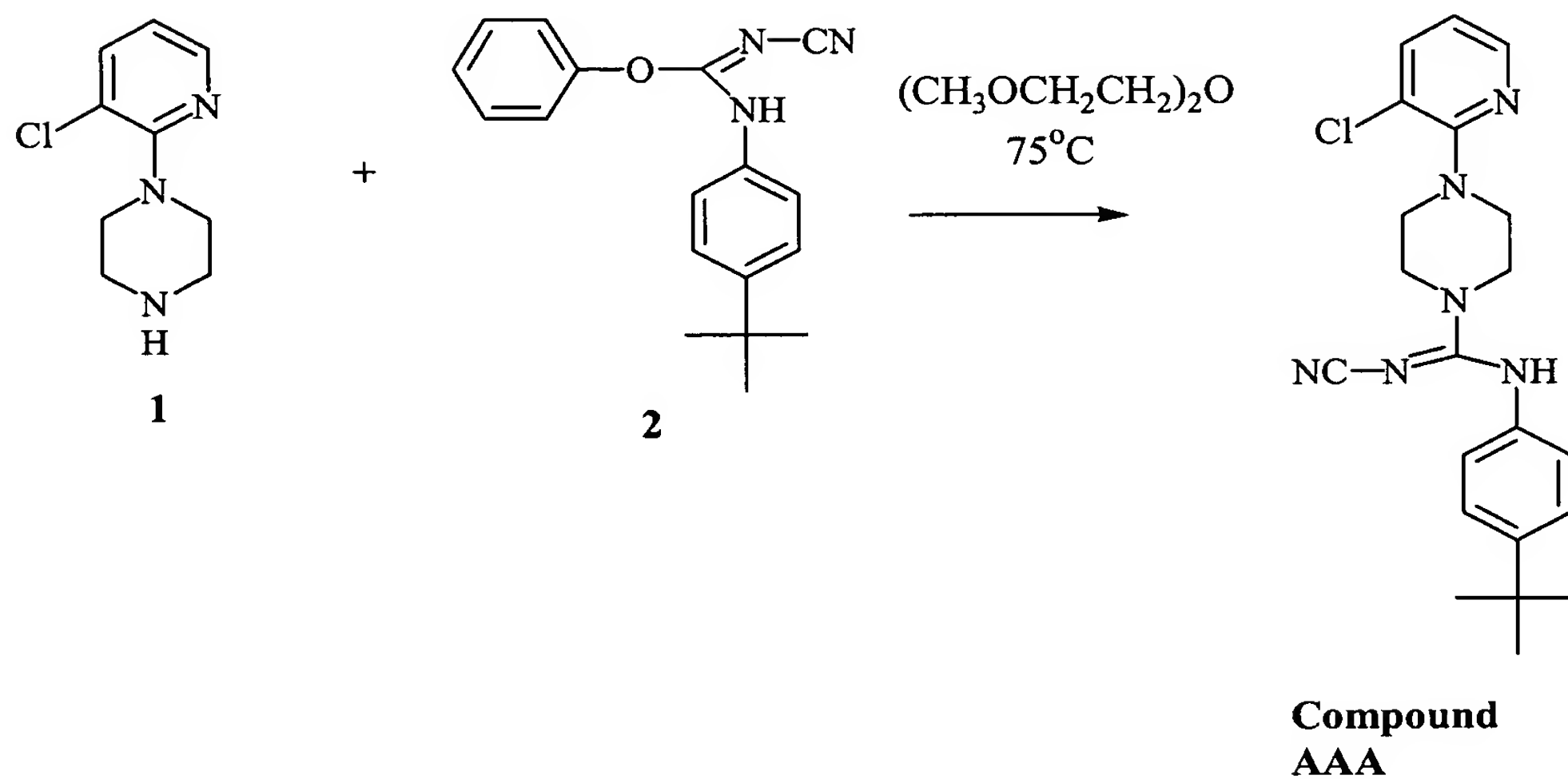
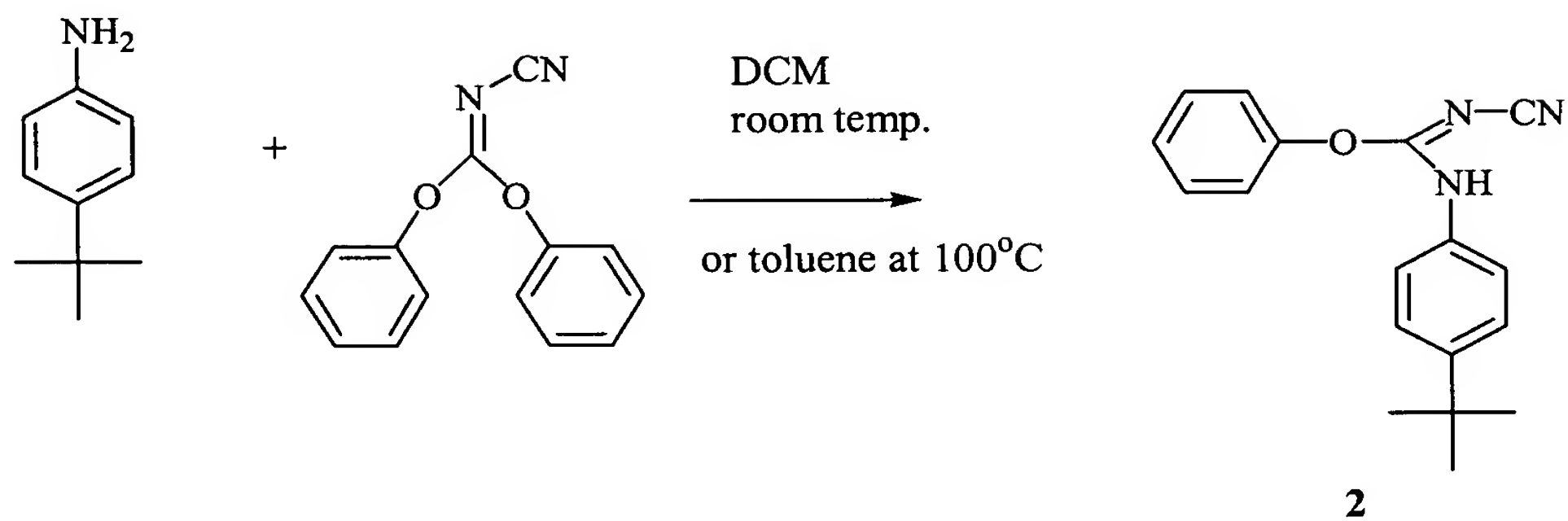
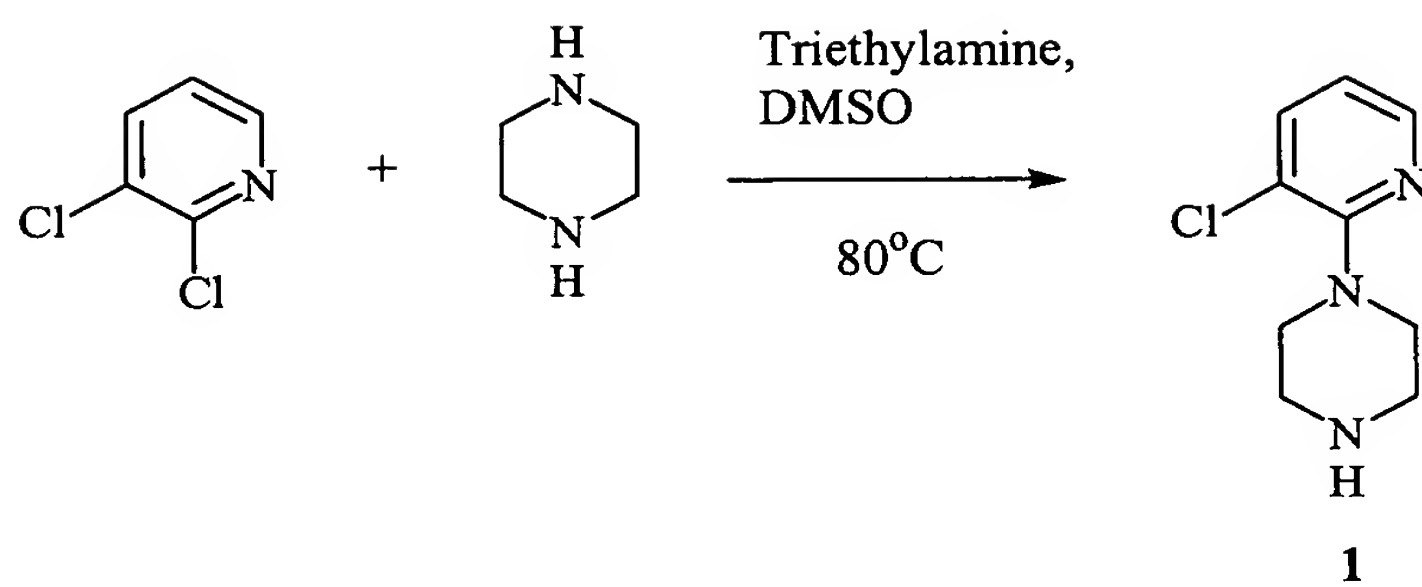
Kits of the invention can further comprise a device that is useful for administering the unit dosage forms. Examples of such a device includes, but are not limited to, a syringe, a drip bag, a patch, an inhaler, and an enema bag.

The following examples are set forth to assist in understanding the invention
10 and should not, of course, be construed as specifically limiting the invention described and claimed herein. Such variations of the invention, including the substitution of all equivalents now known or later developed, which would be within the purview of those skilled in the art, and changes in formulation or minor changes in experimental design, are to be considered to fall within the scope of the invention incorporated herein.
15

5. EXAMPLES

Examples 1-3 relate to the synthesis of illustrative Cyanoiminopiperazine
Compounds.

5.1. Example 1: Synthesis of Compound AAA



2,3-Dichloropyridine (15.0 g, 101.6 mmol), piperazine (9.78 g, 113.70 mmol), and triethylamine (14.36 g, 141.95 mmol) were dissolved in 300 mL of DMSO and the resulting mixture was heated at about 80°C for about 24 h. The reaction mixture was then cooled to room temperature and extracted with a saturated aqueous sodium bicarbonate solution. The organic layer was dried, concentrated, and purified using a silica gel column eluted with a gradient elution from ethyl acetate to 2:1 ethyl acetate:methanol to provide N-(3-chloropyridin-2-yl)-piperazine (compound 1) as a yellow liquid.

A solution diphenylcyanocarbodimide (Commercially available from Sigma-Aldrich, St. Louis, MO (www.sigma-aldrich.com)) (0.5 mmol) and 4-*tert*-butylaniline (0.5 mmol) in 1.5 mL of DCM was stirred at room temperature for about 12 h. The mixture was concentrated under reduced pressure to provide compound 2, which was used directly in the next step without further purification.

A solution of compound 2, prepared as described above, and compound 1 (0.5 mmol), prepared as described above, in 1.5 mL of 2-methoxymethylether was stirred at about 75°C for about 12 h. The solution was cooled to room temperature and purified using direct flash chromatography on a silica gel column eluted with a gradient elution from 1:10 ethyl acetate:hexane to 1:1 ethyl acetate:hexane to provide Compound AAA (62 % yield).

The identity of compound AAA was confirmed using ¹H NMR.

Compound AAA: ¹H NMR (CDCl₃) δ 9.19(dd, J = 1.5, 4.7 Hz, 1H), 6.62 (dd, J = 1.5, 7.8 Hz, 1H), 7.38 (d, J = 8.5 Hz, 2H), 7.18 (b, 1H), 7.01 (d, J = 8.5 Hz, 2H), 6.91 (dd, J = 4.7, 7.8 Hz, 1H), 3.58 (m, 4H), 3.34 (m, 4H), 1.33 (s, 9H) ppm.

5.2. Example 2: Synthesis of Compound AAI

Compound AAI was prepared by a procedure analogous to that used to prepare Compound AAA except that 4-trifluoromethoxyaniline was used in place of 4-*tert*-butylaniline (yield 78%).

The identity of compound AAI was confirmed using ¹H NMR.

Compound AAI: ¹H NMR (CDCl₃) δ 8.19(dd, J = 1.6, 4.7 Hz, 1H), 7.62 (dd, J = 1.6, 7.8 Hz, 1H), 7.26 (b, 1H), 7.24 (d, J = 9.0 Hz, 2H), 7.12 (d, J = 9.0 Hz, 2H), 6.92 (dd, J = 4.7 Hz, 1H), 3.59 (m, 4H), 3.35 (m, 4H) ppm.

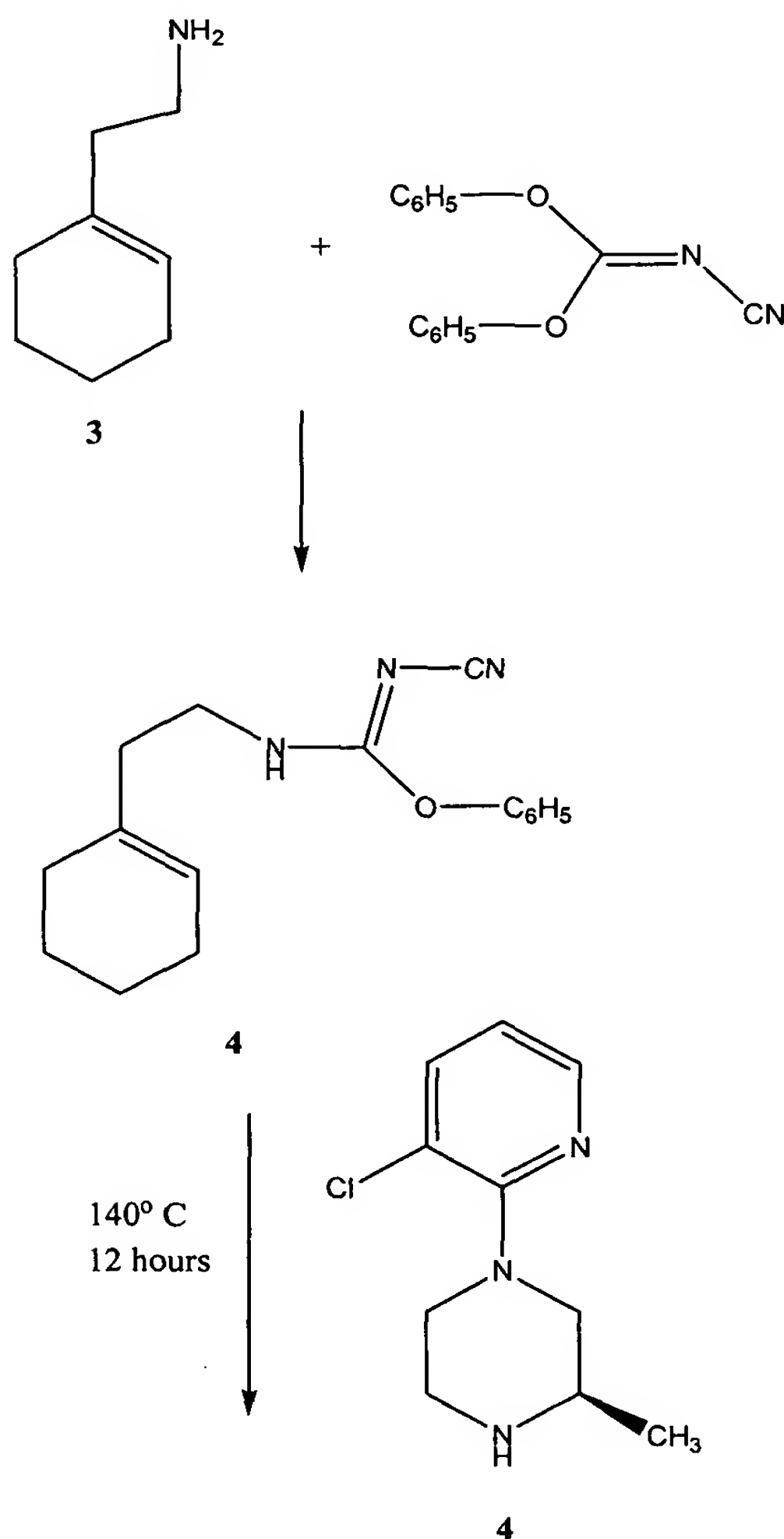
5.3. Example 3: Synthesis of Compound AAG

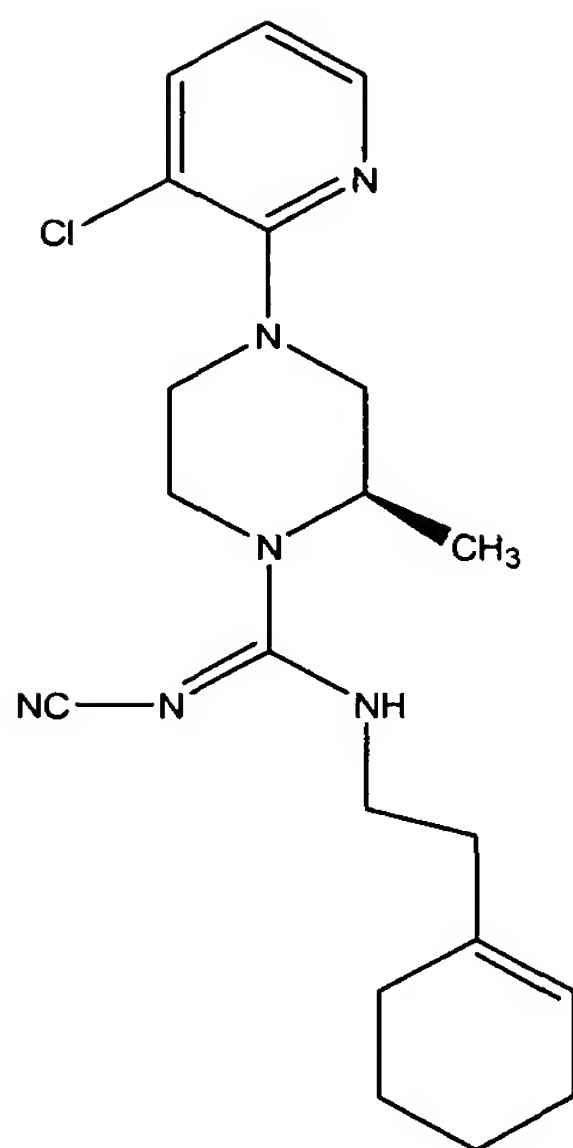
Compound AAG was prepared by a procedure analogous to that used to prepare Compound AAA except that 4-trifluoromethylaniline was used in place of 4-*tert*-butylaniline (yield 61%).

5 The identity of compound AAG was confirmed using ¹H NMR.

Compound AAG: ¹H NMR (CDCl₃) δ 8.19(dd, J = 1.6, 4.7 Hz, 1H), 7.62 (dd, J = 1.6, 7.8 Hz, 1H), 7.26 (b, 1H), 7.24 (d, J = 9.0 Hz, 2H), 7.12 (d, J = 9.0 Hz, 2H), 6.92 (dd, J = 4.7 Hz, 1H), 3.59 (m, 4H), 3.35 (m, 4H) ppm.

10 5.4. Example 4: Synthesis of Compound DEY





Compound DEY

15

To a solution of 2-(1-cyclohexenyl)-ethylamine **3** (125.2 mg, 1.0 mmol) in 2-methoxyethyl ether (2.0 mL) was added diphenylcyanocarbodimide (commercially available from Sigma-Aldrich, St. Louis, MO (www.sigma-aldrich.com)) (238.2 mg, 1.0 mmol) at room temperature. The resultant reaction mixture was heated to about 80° C and allowed to stir at 80° C for about 5 h. (R)-1-(3-chloro-pyridin-2-yl)-3-methylpiperazine **4** (211.6 mg, 1.0 mmol) was added to the reaction mixture and the reaction mixture was heated to about 140° C and allowed to stir at about 140° C for about 12 h. The reaction mixture was then cooled to room temperature and purified using flash chromatography on a silica gel column eluted with ethyl acetate/hexane (10:90 to 50:50) to provide compound **DEY** as a slightly yellow product.

25

Compound **4** was prepared by a procedure analogous to that used to prepare Compound **1**, as described above in Example 1, except that (R)-3-methylpiperazine (commercially available from Sigma-Aldrich, St. Louis, MO (www.sigma-aldrich.com)) was used in place of piperazine.

30

The identity of compound **DEY** was confirmed using ¹H NMR and mass spectroscopy (MS).

Compound **DEY**: ^1H NMR (CDCl_3) δ 8.20 (dd, $J = 1.8, 4.9$ Hz, 1H), 7.63 (dd, $J = 1.8, 7.8$ Hz, 1H), 6.91 (dd, $J = 4.9, 7.8$ Hz, 1H), 5.61 (br, s, 1H), 4.80 (m, 1H), 4.32 (m, 1H), 3.80 (m, 3H), 3.63 (m, 2H), 3.42 (m, 1H), 3.10 (m, 1H), 3.00 (m, 1H), 2.31 (m, 1H), 2.05 (m, 2H), 1.96 (m, 2H), 1.64 (m, 5H), 1.43 (m, 3H) ppm.

5 MS: m/e 387.6

5.5. Example 5: Binding of Cyanoiminopiperazine Compounds to mGluR5

The following assay can be used to demonstrate Cyanoiminopiperazine Compounds that bind to and modulate the activity of mGluR5.

10 Cell cultures: Primary glial cultures are prepared from cortices of Sprague-Dawley 18 days old embryos. The cortices are dissected and then dissociated by trituration. The resulting cell homogenate is plated onto poly-D-lysine precoated T175 flasks (BIOCOAT, commercially available from Becton Dickinson and Company Inc. of Franklin Lakes, NJ) in Dulbecco's Modified Eagle's Medium ("DMEM," pH 7.4), buffered with 25 mM HEPES,
15 and supplemented with 15% fetal calf serum ("FCS," commercially available from Hyclone Laboratories Inc. of Omaha, NE), and incubated at 37°C and 5% CO_2 . After 24 hours, FCS supplementation is reduced to 10%. On day six, oligodendrocytes and microglia are removed by strongly tapping the sides of the flasks. One day following this purification step, secondary astrocyte cultures are established by subplating onto 96 poly-D-lysine precoated
20 T175 flasks (BIOCOAT) at a density of 65,000 cells/well in DMEM and 10% FCS. After 24 hours, the astrocytes are washed with serum free medium and then cultured in DMEM, without glutamate, supplemented with 0.5% FCS, 20 mM HEPES, 10 ng/mL epidermal growth factor ("EGF"), 1 mM sodium pyruvate, and 1X penicillin/streptomycin at pH 7.5 for 3 to 5 days at 37°C and 5% CO_2 . The procedure allows the expression of the mGluR5
25 receptor by astrocytes, as demonstrated by S. Miller *et al.*, *J. Neuroscience* 15(9):6103-6109 (1995).

Assay Protocol: After 3-5 days incubation with EGF, the astrocytes are washed with 127 mM NaCl, 5 mM KCl, 2 mM MgCl_2 , 700 mM NaH_2PO_4 , 2 mM CaCl_2 , 5 mM NaHCO_3 , 8 mM HEPES, 10 mM Glucose at pH 7.4 ("Assay Buffer") and loaded with the dye Fluo-4
30 (commercially available from Molecular Probes Inc. of Eugene, OR) using 0.1 mL of Assay Buffer containing Fluo-4 (3 mM final). After 90 minutes of dye loading, the cells are then washed twice with 0.2 mL Assay Buffer and resuspended in 0.1 mL of Assay Buffer. The

plates containing the astrocytes are then transferred to a Fluorometric Imaging Plate reader (commercially available from Molecular Devices Corporation of Sunnyvale, CA) for the assessment of calcium mobilization flux in the presence of glutamate and in the presence or absence of antagonist. After monitoring fluorescence for 15 seconds to establish a base line, 5 DMSO solutions containing various concentrations of a Cyanoiminopiperazine Compound diluted in Assay Buffer (0.05 mL of 4X dilutions for competition curves) are added to the cell plate and fluorescence is monitored for 2 minutes. 0.05 mL of a 4X glutamate solution (agonist) is then added to each well to provide a final glutamate concentration in each well of 10 mM. Plate fluorescence is then monitored for an additional 60 seconds after agonist 10 addition. The final DMSO concentration in the assay is 1.0%. In each experiment, fluorescence is monitored as a function of time and the data analyzed using Microsoft Excel and GraphPad Prism. Dose-response curves are fit using a non-linear regression to determine IC₅₀ value. In each experiment, each data point is determined two times. The assay results will demonstrate that Cyanoiminopiperazine Compounds bind to and modulate the activity 15 of mGluR5.

5.6 EXAMPLE 6: BINDING OF CYANOIMINOPIPERAZINE COMPOUNDS TO MGLUR5

Alternatively, the following assay can be used to demonstrate that a 20 Cyanoiminopiperazine Compound binds to and modulates the activity of mGluR5.

40,000 CHO-rat mGluR5 cells/well are plated into 96 well plate (Costar 3409, Black, clear bottom, 96 well, tissue culture treated) for an overnight incubation in Dulbecco's Modified Eagle's Medium (DMEM, pH 7.4) and supplemented with glutamine, 10% FBS, 1% Pen/Strep, and 500ug/mL Geneticin. CHO-rat mGluR5 cells are washed and treated with 25 Optimem medium and were incubated for 1-4 hours prior to loading cells. Cell plates are washed with loading buffer (127 mM NaCl, 5 mM KCl, 2 mM MgCl₂, 700 µM Na H₂PO₄, 2 mM CaCl₂, 5 mM NaHCO₃, 8 mM Hepes, and 10 mM glucose, pH 7.4) and incubated with 3µM Fluo 4 (commercially available from Molecular probes Inc. of Eugene, OR) in 0.1 mL of loading buffer. After 90 minutes of dye loading, the cells are washed twice with 0.2 mL 30 loading buffer and resuspended in 0.1 mL loading buffer.

The plates containing the CHO-rat mGluR5 cells are transferred to a Fluorometric Imaging Plate Reader (FLIPR) (commercially available from Molecular Devices Corporation of Sunnyvale, CA) for the assessment of calcium mobilization flux in the presence of glutamate and in the presence or absence of test compounds. After monitoring fluorescence for 15 seconds to establish a baseline, DMSO solutions containing various concentrations of the test compound diluted in loading buffer (0.05 mL of 4X dilutions for the competition curves) are added to the cell plate and fluorescence was monitored for 2 minutes. 0.05 mL of 4X glutamate solution (agonist) is then added to each well to provide a final glutamate concentration in each well of 10 uM. Plate fluorescence is then monitored for an additional 60 seconds after agonist addition. The final DMSO concentration in the assay is 1.0%. In each experiment, fluorescence is monitored as a function of time and the data analyzed using Microsoft Excel and GraphPad Prism. Dose-response curves are fit using a non-linear regression to determine the IC50 value. In each experiment, each data point is determined at least two times.

15

5.7. Example 7: In Vivo Assays for Prevention or Treatment of Pain

Test Animals: Each experiment uses rats weighing between 200-260 g at the start of the experiment. The rats are group-housed and have free access to food and water at all times, except prior to oral administration of a Cyanoiminopiperazine Compound when food is removed for 16 hours before dosing. A control group acts as a comparison to rats treated with a Cyanoiminopiperazine Compound. The control group is administered the carrier for the Cyanoiminopiperazine Compound. The volume of carrier administered to the control group is the same as the volume of carrier and Cyanoiminopiperazine Compound administered to the test group.

Acute Pain: To assess the actions of the Cyanoiminopiperazine Compounds for the treatment or prevention of acute pain the rat tail flick test can be used. Rats are gently restrained by hand and the tail exposed to a focused beam of radiant heat at a point 5 cm from the tip using a tail flick unit (Model 7360, commercially available from Ugo Basile of Italy). Tail flick latencies are defined as the interval between the onset of the thermal stimulus and the flick of the tail. Animals not responding within 20 seconds are removed from the tail flick unit and assigned a withdrawal latency of 20 seconds. Tail flick latencies are measured

25
30

immediately before (pre-treatment) and 1, 3, and 5 hours following administration of a Cyanoiminopiperazine Compound. Data are expressed as tail flick latency(s) and the percentage of the maximal possible effect (% MPE), *i.e.*, 20 seconds, is calculated as follows:

$$\% \text{ MPE} = \frac{[(\text{post administration latency}) - (\text{pre-administration latency})]}{(20 \text{ s pre-administration latency})} \times 100$$

The rat tail flick test is described in F.E. D'Amour *et al.*, "A Method for Determining Loss of Pain Sensation," *J. Pharmacol. Exp. Ther.* 72:74-79 (1941). The results show that Cyanoiminopiperazine Compounds are useful for treating or preventing acute pain.

Acute pain can also be assessed by measuring the animal's response to noxious mechanical stimuli by determining the paw withdrawal threshold ("PWT"), as described below.

Inflammatory Pain: To assess the actions of the Cyanoiminopiperazine Compounds for the treatment or prevention of inflammatory pain the Freund's complete adjuvant ("FCA") model of inflammatory pain is used. FCA-induced inflammation of the rat hind paw is associated with the development of persistent inflammatory mechanical hyperalgesia and provides reliable prediction of the anti-hyperalgesic action of clinically useful analgesic drugs (L. Bartho *et al.*, "Involvement of Capsaicin-sensitive Neurones in Hyperalgesia and Enhanced Opioid Antinociception in Inflammation," *Naunyn-Schmiedeberg's Archives of Pharmacology* 342:666-670 (1990)). The left hind paw of each animal is administered a 50 µL intraplantar injection of 50% FCA. 24 hour post injection, the animal is assessed for response to noxious mechanical stimuli by determining the PWT, as described below. Rats are then administered a single injection of 1, 3, 10 or 30 mg/Kg of either a Cyanoiminopiperazine Compound, 30 mg/Kg of a control selected from indomethacin, Celebrex or naproxen or carrier. Responses to noxious mechanical stimuli are then determined 1, 3, 5, and 24 hours post administration. Percentage reversal of hyperalgesia for each animal is defined as:

30

$$\% \text{ Reversal} = \frac{[(\text{post administration PWT}) - (\text{pre-administration PWT})]}{[(\text{Baseline PWT}) - (\text{pre-administration PWT})]} \times 100$$

- 5 The results show that the Cyanoiminopiperazine Compounds are useful for treating or preventing inflammatory pain.

Neuropathic Pain: To assess the actions of the Cyanoiminopiperazine Compounds for the treatment or prevention of neuropathic pain either the Seltzer model or the Chung model can be used.

- 10 In the Seltzer model, the partial sciatic nerve ligation model of neuropathic pain is used to produce neuropathic hyperalgesia in rats (Z. Seltzer *et al.*, “A Novel Behavioral Model of Neuropathic Pain Disorders Produced in Rats by Partial Sciatic Nerve Injury,” *Pain* 43:205-218 (1990)). Partial ligation of the left sciatic nerve is performed under isoflurane/O₂ inhalation anaesthesia. Following induction of anesthesia, the left thigh of the rat is shaved
- 15 and the sciatic nerve exposed at high thigh level through a small incision and is carefully cleared of surrounding connective tissues at a site near the trochanter just distal to the point at which the posterior biceps semitendinosus nerve branches off of the common sciatic nerve. A 7-0 silk suture is inserted into the nerve with a 3/8 curved, reversed-cutting mini-needle and tightly ligated so that the dorsal 1/3 to 1/2 of the nerve thickness is held within the ligature.
- 20 The wound is closed with a single muscle suture (4-0 nylon (Vicryl)) and a Vetbond surgical glue. Following surgery, the wound area is dusted with antibiotic powder. Sham-treated rats undergo an identical surgical procedure except that the sciatic nerve is not manipulated. Following surgery, animals are weighed and placed on a warm pad until they recover from anesthesia. Animals are then returned to their home cages until behavioral testing begins.
- 25 The animal is assessed for response to noxious mechanical stimuli by determining PWT, as described below, prior to surgery (baseline), then immediately prior to and 1, 3, and 5 hours after drug administration for the left rear paw of the animal. Percentage reversal of neuropathic hyperalgesia is defined as:

$$\% \text{ Reversal} = \frac{[(\text{post administration PWT}) - (\text{pre-administration PWT})]}{[(\text{Baseline PWT}) - (\text{pre-administration PWT})]} \times 100$$

5 In the Chung model, the spinal nerve ligation model of neuropathic pain is used to produce mechanical hyperalgesia, thermal hyperalgesia and tactile allodynia in rats. Surgery is performed under isoflurane/O₂ inhalation anaesthesia. Following induction of anaesthesia a 3 cm incision is made and the left paraspinal muscles are separated from the spinous process at the L₄ - S₂ levels. The L₆ transverse process is carefully removed with a pair of small
10 rongeurs to identify visually the L₄ - L₆ spinal nerves. The left L₅ (or L₅ and L₆) spinal nerve(s) is isolated and tightly ligated with silk thread. A complete hemostasis is confirmed and the wound is sutured using non-absorbable sutures, such as nylon sutures or stainless steel staples. Sham-treated rats undergo an identical surgical procedure except that the spinal nerve(s) is not manipulated. Following surgery animals are weighed, administered a
15 subcutaneous (s.c.) injection of saline or ringers lactate, the wound area is dusted with antibiotic powder and they are kept on a warm pad until they recover from the anesthesia. Animals are then returned to their home cages until behavioral testing begins. The animals are assessed for response to noxious mechanical stimuli by determining PWT, as described below, prior to surgery (baseline), then immediately prior to and 1, 3, and 5 hours after being
20 administered a Cyanoiminopiperazine Compound for the left rear paw of the animal. The animal can also be assessed for response to noxious thermal stimuli or for tactile allodynia, as described below. The Chung model for neuropathic pain is described in S.H. Kim, "An Experimental Model for Peripheral Neuropathy Produced by Segmental Spinal Nerve Ligation in the Rat," *Pain* 50(3):355-363 (1992). The results will show that
25 Cyanoiminopiperazine Compounds are useful for treating or preventing neuropathic pain.

Response to Mechanical Stimuli as an Assessment of Mechanical Hyperalgesia: The paw pressure assay can be used to assess mechanical hyperalgesia. For this assay, hind paw withdrawal thresholds (PWT) to a noxious mechanical stimulus are determined using an analgesymeter (Model 7200, commercially available from Ugo Basile of Italy) as described in
30 C. Stein, "Unilateral Inflammation of the Hindpaw in Rats as a Model of Prolonged Noxious Stimulation: Alterations in Behavior and Nociceptive Thresholds," *Pharmacology*

Biochemistry and Behavior 31:451-455 (1988). The maximum weight that can be applied to the hind paw is set at 250 g and the end point is taken as complete withdrawal of the paw. PWT is determined once for each rat at each time point and only the affected (ipsilateral) paw is tested.

- 5 Response to Thermal Stimuli as an Assessment of Thermal Hyperalgesia: The plantar test can be used to assess thermal hyperalgesia. For this test, hind paw withdrawal latencies to a noxious thermal stimulus are determined using a plantar test apparatus (commercially available from Ugo Basile of Italy) following the technique described by K. Hargreaves *et al.*, “A New and Sensitive Method for Measuring Thermal Nociception in Cutaneous
- 10 Hyperalgesia,” *Pain* 32(1):77-88 (1988). The maximum exposure time is set at 32 seconds to avoid tissue damage and any directed paw withdrawal from the heat source is taken as the end point. Three latencies are determined at each time point and averaged. Only the affected (ipsilateral) paw is tested.

- Assessment of Tactile Allodynia: To assess tactile allodynia, rats are placed in clear,
- 15 plexiglass compartments with a wire mesh floor and allowed to habituate for a period of at least 15 minutes. After habituation, a series of von Frey monofilaments are presented to the plantar surface of the left (operated) foot of each rat. The series of von Frey monofilaments consists of six monofilaments of increasing diameter, with the smallest diameter fiber presented first. Five trials are conducted with each filament with each trial separated by
- 20 approximately 2 minutes. Each presentation lasts for a period of 4-8 seconds or until a nociceptive withdrawal behavior is observed. Flinching, paw withdrawal or licking of the paw are considered nociceptive behavioral responses.

5.8. Example 8: *In Vivo* Assays for Prevention or Treatment of Anxiety

- 25 The elevated plus maze test or the shock-probe burying test can be used to assess the anxiolytic activity of Cyanoiminopipereazine Compounds in rats or mice.

- The Elevated Plus Maze Test: The elevated plus maze consists of a platform with 4 arms, two open and two closed (50x10x50 cm enclosed with an open roof). Rats (or mice) are placed in the center of the platform, at the crossroad of the 4 arms, facing one of the
- 30 closed arms. Time spent in the open arms vs the closed arms and number of open arm entries

during the testing period are recorded. This test is conducted prior to drug administration and again after drug administration. Test results are expressed as the mean time spent in open arms and the mean number of entries into open arms. Known anxiolytic drugs increase both the time spent in open arms and number of open arm entries. The elevated plus maze test is described in D. Treit, "Animal Models for the Study of Anti-anxiety Agents: A Review," *Neuroscience & Biobehavioral Reviews* 9(2):203-222 (1985).

The Shock-Probe Burying Test: For the shock-probe burying test the testing apparatus consists of a plexiglass box measuring 40x30x40 cm, evenly covered with approximately 5 cm of bedding material (odor absorbent kitty litter) with a small hole in one end through which a shock probe (6.5 cm long and 0.5 cm in diameter) is inserted. The plexiglass shock probe is helically wrapped with two copper wires through which an electric current is administered. The current is set at 2 mA. Rats are habituated to the testing apparatus for 30 min on 4 consecutive days without the shock probe in the box. On test day, rats are placed in one corner of the test chamber following drug administration. The probe is not electrified until the rat touches it with its snout or fore paws, at which point the rat receives a brief 2 mA shock. The 15 min testing period begins once the rat receives its first shock and the probe remains electrified for the remainder of the testing period. The shock elicits burying behavior by the rat. Following the first shock, the duration of time the rat spends spraying bedding material toward or over the probe with its snout or fore paws (burying behavior) is measured as well as the number of contact-induced shocks the rat receives from the probe. Known anxiolytic drugs reduce the amount of burying behavior. In addition, an index of the rat's reactivity to each shock is scored on a 4 point scale. The total time spent immobile during the 15 min testing period is used as an index of general activity. The shock-probe burying test is described in D. Treit, 1985, *supra*. The results of this test will demonstrate that Cyanoiminopipereazine Compounds are useful for treating or preventing anxiety.

5.9. Example 9: *In Vivo* Assays for Prevention or Treatment of an Addictive Disorder

The conditioned place preference test or drug self-administration test can be used to assess the ability of Cyanoiminopipereazine Compounds to attenuate the rewarding properties of known drugs of abuse.

The Conditioned Place Preference Test: The apparatus for the conditioned place preference test consists of two large compartments (45x45x30 cm) made of wood with a plexiglass front wall. These two large compartments are distinctly different. Doors at the back of each large compartment lead to a smaller box (36x18x20 cm) box made of wood, painted grey, with a ceiling of wire mesh. The two large compartments differ in terms of shading (white vs black), level of illumination (the plexiglass door of the white compartment is covered with aluminum foil except for a window of 7x7 cm), texture (the white compartment has a 3 cm thick floor board (40x40 cm) with nine equally spaced 5 cm diameter holes and the black has a wire mesh floor), and olfactory cues (saline in the white compartment and 1 mL of 10% acetic acid in the black compartment). On habituation and testing days, the doors to the small box remain open, giving the rat free access to both large compartments.

The first session that a rat is placed in the apparatus is a habituation session and entrances to the smaller grey compartment remain open giving the rat free access to both large compartments. During habituation, rats generally show no preference for either compartment. Following habituation, rats are given 6 conditioning sessions. Rats are divided into 4 groups: carrier pre-treatment + carrier (control group), Cyanoiminopipereazine Compound pre-treatment + carrier, carrier pre-treatment + morphine, Cyanoiminopipereazine Compound pre-treatment + morphine. During each conditioning session the rat is injected with one of the drug combinations and confined to one compartment for 30 min. On the following day, the rat receives a carrier + carrier treatment and is confined to the other large compartment. Each rat receives three conditioning sessions consisting of 3 drug combination-compartment and 3 carrier-compartment pairings. The order of injections and the drug/compartment pairings are counterbalanced within groups. On the test day, rats are injected prior to testing (30 min to 1 hour) with either morphine or carrier and the rat is placed in the apparatus, the doors to the grey compartment remain open and the rat is allowed to explore the entire apparatus for 20 min. The time spent in each compartment is recorded. Known drugs of abuse increase the time spent in the drug-paired compartment during the testing session. If the Cyanoiminopipereazine Compound blocks the acquisition of morphine conditioned place preference (reward), there will be no difference in time spent in each side in rats pre-treated with a Cyanoiminopipereazine Compound and the group will not be

different from the group of rats that was given carrier + carrier in both compartments. Data will be analyzed as time spent in each compartment (drug combination-paired vs carrier-paired). Generally, the experiment is repeated with a minimum of 3 doses of a Cyanoiminopipereazine Compound.

5 The Drug Self-Administration Test: The apparatus for the drug self-administration test is a standard commercially available operant conditioning chamber. Before drug trials begin rats are trained to press a lever for a food reward. After stable lever pressing behavior is acquired, rats are tested for acquisition of lever pressing for drug reward. Rats are implanted with chronically indwelling jugular catheters for i.v. administration of
10 compounds and are allowed to recover for 7 days before training begins. Experimental sessions are conducted daily for 5 days in 3 hour sessions. Rats are trained to self-administer a known drug of abuse, such as morphine. Rats are then presented with two levers, an “active” lever and an “inactive” lever. Pressing of the active lever results in drug infusion on a fixed ratio 1 (FR1) schedule (*i.e.*, one lever press gives an infusion) followed by a 20
15 second time out period (signaled by illumination of a light above the levers). Pressing of the inactive lever results in infusion of excipient. Training continues until the total number of morphine infusions stabilizes to within $\pm 10\%$ per session. Trained rats are then used to evaluate the effect of Cyanoiminopipereazine Compounds pre-treatment on drug self-administration. On test day, rats are pre-treated with a Cyanoiminopipereazine Compound or
20 excipient and then are allowed to self-administer drug as usual. If the Cyanoiminopipereazine Compound blocks the rewarding effects of morphine, rats pre-treated with the Cyanoiminopipereazine Compound will show a lower rate of responding compared to their previous rate of responding and compared to excipient pre-treated rats. Data is analyzed as the change in number of drug infusions per testing session (number of infusions
25 during test session – number of infusions during training session). The results will demonstrate that Cyanoiminopipereazine Compounds are useful for treating or preventing an addictive disorder.

5.10. Example 10: Functional Assay for Characterizing mGluR 1 Antagonistic Properties

30 Functional assays for the characterization of mGluR1 antagonistic properties are well known in the art. For example, the following procedure can be used.

cDNA encoding rat mGluR1a receptor is obtained from, *e.g.*, Prof. S. Nakanishi (Kyoto, Japan). It is transiently transfected into HEK-EBNA cells using a procedure described by Schlaeger *et al.*, *New Dev. New Appl. Anim. Cell Techn.*, Proc. ESACT Meet., 15th (1998), 105-112 and 117-120. [Ca²⁺] measurements are performed on mGluR1a transfected HEK-EBNA cells after incubation of the cells with Fluo-3 AM (0.5 µM final concentration) for 1 hour at 37°C followed by 4 washes with assay buffer (DMEM supplemented with Hank's salt and 20 mM HEPES. [Ca²⁺] measurements are done using a fluorometric imaging plate reader, *e.g.*, FLIPR from Molecular Devices Corporation, La Jolla, CA. 10 µM glutamate as agonist is used to evaluate the potency of the antagonists.

10 Increasing concentrations of antagonists are applied to the cells 5 minutes prior to application of the agonist. The inhibition (antagonists) curves are fitted with appropriate software, for example, the four-parameter logistic equation giving IC₅₀ and Hill coefficient using the iterative nonlinear curve fitting software Origin from Microcal Software Inc., Northampton, MA. The results of this assay will demonstrate that Cyanoiminopiperazine

15 Compounds bind to and modulate the activity of mGluR1.

5.11. Example 11: Binding of Cyanoiminopiperazine Compounds to VR1

Methods for assaying compounds capable of inhibiting VR1 are well known to those skilled in the art, for example, those methods disclosed in U.S. Patent No. 6,239,267 to Duckworth *et al.*; U.S. Patent No. 6,406,908 to McIntyre *et al.*; or U.S. Patent No. 6,335,180 to Julius *et al.* The results of these assays will demonstrate that Cyanoiminopiperazine Compounds bind to and modulate the activity of VR1.

Binding of Compound DEY to VR1: Assay Protocol

Human VR1 cloning. Human spinal cord RNA (commercially available from Clontech, Palo Alto, CA) was used. Reverse transcription was conducted on 1.0 µg total RNA using Thermoscript Reverse Transcriptase (commercially available from Invitrogen, Carlsbad, CA) and oligo dT primers as detailed in its product description. Reverse transcription reactions were incubated at 55°C for 1 h, heat-inactivated at 85°C for 5 min, and RNase H-treated at 37°C for 20 min.

Human VR1 cDNA sequence was obtained by comparison of the human genomic sequence, prior to annotation, to the published rat sequence. Intron sequences were removed and flanking exonic sequences were joined to generate the hypothetical human cDNA. Primers flanking the coding region of human VR1 were designed as follows: forward
5 primer, GAAGATCTTCGCTGGTTGCACACTGGGCCACA; and reverse primer, GAAGATCTTCGGGGACAGTGACGGTTGGATGT.

PCR of VR1 was performed on one tenth of the Reverse transcription reaction mixture using Expand Long Template Polymerase and Expand Buffer 2 in a final volume of 50 μ L according to the manufacturer's instructions (Roche Applied Sciences, Indianapolis,
10 IN). After denaturation at 94°C for 2 min PCR amplification was performed for 25 cycles at 94°C for 15 sec, 58°C for 30 sec, and 68°C for 3 min followed by a final incubation at 72°C for 7 min to complete the amplification. A PCR product of ~2.8 kb was gel-isolated using a 1.0% agarose, Tris-Acetate gel containing 1.6 μ g/mL of crystal violet and purified with a S.N.A.P. UV-Free Gel Purification Kit (commercially available from Invitrogen). The VR1
15 PCR product was cloned into the pIND/V5-His-TOPO vector (commercially available from Invitrogen) according to the manufacturer's instructions. DNA preparations, restriction enzyme digestions, and preliminary DNA sequencing were performed according to standard protocols. Full-length sequencing confirmed the identity of the human VR1.

Generation of inducible cell lines. Unless noted otherwise, cell culture
20 reagents were purchased from Life Technologies of Rockville, MD. HEK293-EcR cells expressing the ecdysone receptor (commercially available from Invitrogen) were cultured in Growth Medium (Dulbecco's Modified Eagles Medium containing 10% fetal bovine serum (commercially available from HYCLONE, Logan, UT), 1x penicillin/streptomycin, 1x glutamine, 1 mM sodium pyruvate and 400 μ g/mL Zeocin (commercially available from
25 Invitrogen)). The VR1-pIND constructs were transfected into the HEK293-EcR cell line using Fugene transfection reagent (commercially available from Roche Applied Sciences, Basel, Switzerland). After 48 h, cells were transferred to Selection Medium (Growth Medium containing 300 μ g/mL G418 (commercially available from Invitrogen)). Approximately 3 weeks later individual Zeocin/G418 resistant colonies were isolated and
30 expanded. To identify functional clones, multiple colonies were plated into 96-well plates and expression was induced for 48 h using Selection Medium supplemented with 5 μ M

ponasterone A (“PonA”) (commercially available from Invitrogen). On the day of assay, cells were loaded with Fluo-4 (a calcium-sensitive dye that is commercially available from Molecular Probes, Eugene, OR) and CAP-mediated calcium influx was measured using a Fluorometric Imaging Plate Reader (“FLIPR”) (commercially available from Molecular Devices Corp., Sunnyvale, CA) as described below. Functional clones were re-assayed, expanded, and cryopreserved.

pH-Based Assay. Two days prior to performing this assay, cells were seeded on poly-D-lysine-coated 96-well clear-bottom black plates (commercially available from Becton-Dickinson) at 75,000 cells/well in growth media containing 5 μ M PonA (commercially available from Invitrogen) to induce expression. On the day of the assay, the plates were washed with 0.2 mL 1x Hank’s Balanced Salt Solution (commercially available from Life Technologies) containing 1.6 mM CaCl_2 and 20 mM HEPES, pH 7.4 (“wash buffer”), and loaded using 0.1 mL of wash buffer containing Fluo-4 (3 μ M final concentration, commercially available from Molecular Probes). After 1 h, the cells were washed twice with 0.2 mL wash buffer and resuspended in 0.05 mL 1x Hank’s Balanced Salt Solution (commercially available from Life Technologies) containing 3.5 mM CaCl_2 and 10 mM Citrate, pH 7.4 (“assay buffer”). Plates were then transferred to a FLIPR (commercially available from Molecular Devices) for assay. Compound **DEY** was diluted in assay buffer, and 50 μ L of the resultant solution were added to the cell plates and the solution monitored for two minutes. The final concentration of Compound **DEY** ranged from about 50 pM to about 3 μ M. Agonist buffer (wash buffer titrated with 1N HCl to provide a solution having a pH of 5.5 when mixed 1:1 with assay buffer) (0.1 mL) was then added to each well, and the plates were incubated for 1 additional minute. Data were collected over the entire time course and analyzed using Excel and Graph Pad Prism. Compound **DEY** when assayed according to this protocol had an IC_{50} of 196.7 ± 39.8 nM (n + 3).

Capsaicin-based Assay. Two days prior to performing this assay, cells were seeded in poly-D-lysine-coated 96-well clear-bottom black plates (50,000 cells/well) in growth media containing 5 μ M PonA (commercially available from Invitrogen) to induce expression. On the day of the assay, the plates were washed with 0.2 mL 1x Hank's Balanced Salt Solution (commercially available from Life Technologies) containing 1 mM CaCl_2 and 20 mM HEPES, pH 7.4, and cells were loaded using 0.1 mL of wash buffer containing Fluo-4

(3 μ M final). After one hour, the cells were washed twice with 0.2 mL of wash buffer and resuspended in 0.1 mL of wash buffer. The plates were transferred to a FLIPR (commercially available from Molecular Devices) for assay. 50 μ L of Compound **DEY** diluted with assay buffer were added to the cell plates and incubated for 2 min. The final concentration of
5 Compound **DEY** ranged from about 50 pM to about 3 μ M. Human VR1 was activated by the addition of 50 μ L of capsaicin (400 nM), and the plates were incubated for an additional 3 min. Data were collected over the entire time course and analyzed using Excel and GraphPad Prism. Compound **DEY** when assayed according to this protocol had an IC_{50} of 59.4 ± 13.1 nM (n + 3).

10 The results of the pH-based assay and the capsaicin-based assay demonstrate that Compound **DEY**, an illustrative Cyanoiminopiperazine Compound, binds to and modulates the activity of human VR1.

 The present invention is not to be limited in scope by the specific embodiments disclosed in the examples which are intended as illustrations of a few aspects of
15 the invention and any embodiments that are functionally equivalent are within the scope of this invention. Indeed, various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art and are intended to fall within the scope of the appended claims.

 A number of references have been cited, the entire disclosures of which are
20 incorporated herein by reference.